Journal of
CHRONIC DISEASES

VOL. 5 JUNE, 1957 NO. 6

VOL.
5
1957

SYMPOSIUM

Rheumatoid Arthritis

Special Editor

Joseph J. Bunim

INTRODUCTORY STATEMENT TO SYMPOSIUM ON RHEUMATOID ARTHRITIS

SIGNIFICANT additions to the body of knowledge related to rheumatoid arthritis have been made during the years of the past decade. These advances are reflected in the new terms appearing in the vocabulary of the disease; e.g., rheumatoid heart disease, rheumatoid arteritis, sensitized sheep cell agglutination, cortisone therapy, and L.E. phenomenon. Ten years ago the subcutaneous nodule was considered an "avascular granuloma" and the prevalence of rheumatoid arthritis in this country was unknown. It was inconceivable then that the acute inflammatory manifestations of many of the rheumatic diseases would subside promptly upon administration of certain adrenal corticosteroids.

This symposium on rheumatoid arthritis summarizes and critically appraises the knowledge gained during these recent years. It begins with a provocative and illuminating review of the many diverse concepts and speculations on the etiology of rheumatoid arthritis. This paper emphasizes the probable significance of the presence in the serum of patients with this disease of a "specific" substance which causes agglutination of sensitized sheep erythrocytes.

The extensive information on this serologic reaction is masterfully analyzed in another paper. When erythrocytes from sheep (or other species) are coated with specific rabbit antiserum or with normal human gamma globulin and then mixed with diluted serum from a patient with peripheral rheumatoid arthritis,

agglutination occurs. Before testing, the serum is absorbed with normal sheep erythrocytes. Hemagglutination does not take place when similarly treated serum, from normal subjects or from patients with other types of arthritis, is tested. (The agglutination test may be positive, however, in a proportion of cases of systemic lupus erythematosus, polyarteritis nodosa, or scleroderma.) The substance in the positively reacting serum responsbile for the agglutination is referred to as the "rheumatoid factor." The erythrocytes in the system act simply as an inert carrier for the gamma globulin present in the human serum or rabbit antiserum. Other particulate matter such as bacteria or synthetic polymers (latex particles) may be substituted for erythrocytes in this test. Several methods of varying complexity, specificity, and sensitivity, currently in use, are described in the paper. An appraisal of the relative merits of these tests, their usefulness and implications are also discussed.

Workers in many laboratories are now engaged in studies attempting to determine more definite data: whether the rheumatoid factor consists of several components; the nature of its chemical structure and physical characteristics; its biologic properties; whether it is an antibody, an enzyme, or possibly a complement; and, of prime importance, whether it contributes to or results from the inflammatory process in rheumatoid arthritis.

Surprisingly, although rheumatoid arthritis was clearly distinguished from osteoarthritis one-half century ago, precise and standardized criteria for the diagnosis of rheumatoid arthritis were not established until this year. The criteria for "definite," "probable," and "possible" rheumatoid arthritis have been defined and validated by a Committee of the American Rheumatism Association and are published in this symposium. The first satisfactory study, based on these criteria, of the occurrence of rheumatoid arthritis in an American community is reported here. The prevalence at any one time of definite and probable rheumatoid arthritis in persons above the age of 14 is 2.7 per cent, and in any given year at least 5 per cent of the population, in the district studied, have an attack of this type of arthritis.

That rheumatoid arthritis is a systemic disease and is not limited to the structures of the joints, has long been evident. Indeed, several workers have suggested that the name be changed from rheumatoid arthritis to "rheumatoid disease." Nevertheless, the occurrence of significant inflammatory changes in the arteries of patients with rheumatoid arthritis (rheumatoid arteritis) was not recognized until 1951. In the paper on "Vascular Lesions in Rheumatoid Arthritis," evidence is presented to show that vasculitis is a conspicuous feature of the development of subcutaneous nodules and, moreover, that disseminated arteritis involving synovial lining, skeletal muscle, peripheral nerves, brain, heart, and other viscera may occur in some cases. It is suggested that polyarteritis nodosa (by which term is meant necrotizing angiitis) in rheumatoid arthritis is an exaggerated form of rheumatoid arteritis and not an independent lesion.

Since vasculitis is also an integral feature of systemic lupus erythematosus and classical polyarteritis nodosa, the question arises as to what is the relationship of rheumatoid arthritis to these collagen diseases. Certainly it is important to differentiate among these illnesses since their treatment and prognosis depend on the diagnosis. Beyond such practical considerations, however, is a provocative

question. What are the etiologic or pathogenetic implications of the vascular lesion which apparently links rheumatoid arthritis to the collagen diseases? Of considerable concern to the clinician is the relationship of prolonged steroid therapy to the activation or accentuation of the arterial lesions and also to the apparently rising incidence of polyarteritis nodosa in patients with rheumatoid arthritis. These problems are discussed in several papers of this symposium.

There is unanimity of opinion that treatment of the patient with rheumatoid arthritis should be comprehensive, individualized, and, in the beginning, conservative. What these overworked but meaningful words imply is fully specified in three papers of this collection by workers who have had many years of intensive experience with rheumatic diseases and who have consistently exercised critical judgment in appraising the value and limitations of a conservative program of treatment. The results obtained by simple medical, physical, and orthopedic measures serve as yardsticks by which more potent agents are evaluated. Approximately 50 per cent of the patients treated conservatively and followed for about ten years are either improved, markedly improved, or in remission.

The less fortunate half of the patients who fail to improve or who become progressively worse despite skillful conservative treatment confront the physician with a challenging problem to which there is no simple or entirely safe solution. In these cases the clinician will resort generally to one of the more potent antirheumatic agents; gold compounds, adrenocortical steroids or their synthetic analogues, or phenylbutazone. He will do so cognizant that these drugs suppress but do not arrest the disease and, like the conservative regimen, do not significantly alter the ultimate course of rheumatoid arthritis. Yet, administration of these compounds results in considerable benefit to the patient, impressively increases his functional capacity, and facilitates and accelerates his rehabilitation. The administration of each of these agents is associated, however, with potential hazard and the physician must estimate whether the anticipated gains in each case exceed the risks of serious, adverse side effects. To help in this decision, the benefits and toxicity observed with each of these potent agents are carefully analyzed and evaluated by several clinical investigators of long experience.

The final paper reports experience with a program in which patients with arthritis return to gainful occupation under competitive conditions. Success in 40 per cent of the cases is reported. Serious functional impairment, middle age, and long duration of arthritis, surprisingly, do not preclude return to employment, provided the patient is properly motivated, can endure regular work, and is guided by a team of interested and competent counselors. Incidentally, it is discouraging to note how few private physicians avail themselves of the help offered to their arthritic patients by vocational rehabilitation agencies.

While it is true that little is known about the etiology and pathogenesis of rheumatoid arthritis and that a cure for this crippling disease remains elusive, it is none the less important that what *is* known about this illness should be effectively applied and that the measures proved to be of therapeutic value be administered as soon after onset as possible. It is hoped that this symposium will contribute to the attainment of this end.

JOSEPH J. BUNIM, M.D.
Bethesda, Md.

SOME CURRENT CONCEPTS OF THE ETIOLOGY OF RHEUMATOID ARTHRITIS

ELLIS DRESNER, M.D., M.R.C.P.

BOSTON, MASS.

From the Department of Medicine, Lemuel Shattuck Hospital, Boston, Mass.

(Received for publication Dec. 1, 1956.)

VOL
5
195

UNTIL the last decade, interest in the rheumatic diseases (with the exception of rheumatic fever) was dormant except for the few physicians practicing in this field. The reason for disinterest in these diseases was a lack of knowledge of their basic pathology, etiology, and pathogenesis, and the absence of a logical nosologic classification. That rheumatic diseases are now provoking widespread interest and study can be ascribed to the work of Klinge in the early 1930's, who first drew attention to the systemic character of the connective tissue lesions in rheumatic fever and their similarity to the tissue changes in the hyperergic state; to the work of Klemperer in the 1940's, who first perceived the nosologic unity of the "collagen-vascular" group of disorders; and, finally, to Hench's discovery of the therapeutic efficacy of cortical steroid hormones in their treatment.

The investigations into the causal mechanisms of the rheumatic diseases stimulated by these new lines of thought have been hampered by an almost total ignorance of the physiology, pathology, and reactivity of the tissues concerned. Immense strides have been made in a very short time in remedying this deficiency, and connective tissue metabolism, an unknown field a few years ago, is now being actively explored by an amazingly wide range of biochemical, biophysical, enzymatic, and histochemical techniques. Much new knowledge has been acquired but the study is still in an analytical stage and insufficient data have as yet accrued to permit the synthesis of formal concepts of pathogenetic mechanisms in connective tissue diseases.

Many of today's etiologic hypotheses of rheumatoid arthritis are still based on uncritical clinical impressions, but there are some which, although far from being proved, have some weight of scientific evidence to support them. These concepts include disordered adrenocortical function, disordered hepatic metabolism, and the hyperimmune state. The evidence on which each is based will be examined, and, in addition, the possible etiologic implications of the sheep cell agglutination test, the most important finding since rheumatoid arthritis was first described as a separate disease entity, will be discussed.

OL.
5
957

THEORY OF ADRENOCORTICAL DYSFUNCTION

It is only within the last decade that the attention of investigators into the cause of rheumatoid arthritis has been focused on the adrenal cortex in an attempt to ascertain whether a functional disturbance of this gland, or of its response to pituitary stimulation, is responsible for the rheumatoid state. This line of investigation was instigated largely by the discovery of the clinical effectiveness of corticotropin and of cortisone and its analogues in rheumatoid arthritis and other rheumatic diseases.

It soon became apparent that the action of steroid hormones in arthritis is not due to a deficient output of cortisone-like steroids by the adrenals; hormone therapy is not replacement therapy in this disease. Electrolyte balance is maintained, there is no impairment of potassium tolerance,[65] and the adrenal response to corticotropin and adrenalin is, in all respects, normal[116] even after years of cortisone administration.[42] The association of rheumatoid arthritis with clinical adrenocortical deficiency is rare and probably fortuitous. When it does occur both the arthritis and the Addison's disease respond to cortisone in the usual way.[20, 36] The administration of deoxycortone to patients with Addison's disease is said to provoke the onset of arthritis alleviated by cortisone,[44] but DCA is a nonphysiologic steroid, and there are no reports of replacement therapy with aldosterone causing such a syndrome. The adrenals are structurally normal in rheumatoid arthritis[108] and blood levels of corticosteroids are within normal limits.[87, 92]

Intensive study is being made of the urinary excretion of steroid metabolites in rheumatoid arthritis as a means of assessing adrenocortical function. The over-all average excretion by the adrenal of neutral 17-ketosteroids is generally reported as being normal, but low normal and subnormal levels have been found, these generally not differing from the low levels found in other chronic, debilitating diseases. A low mean level of urinary reducing steroids has been reported by one group of workers[62] but others have found no significant alteration in this respect.[58, 111]

Although there may be no evidence of abnormality in the urinary excretion of total neutral 17-ketosteroids or 11-oxycorticosteroids, this does not necessarily imply that there is no adnormality in the metabolism or secretion of the C_{21} group of steroids by the adrenal, and new techniques for the fractionation and separation of urinary steroids are being elaborated to determine patterns of steroid excretion more precisely. Devis[30] performed differential analysis of the urinary 17-ketosteroids in rheumatoid arthritis and found, in 10 out of 15 cases, a decrease in the proportion of 11-deoxy-17-ketosteroids. Fractionation studies by Kellie and Wade[67] revealed an increased ratio of etiocholanolone to androsterone in the urines of three patients with rheumatoid arthritis, in whom the administration of corticotropin caused a reversion of this ratio to normal, as well as an increased excretion of all the fractions. However, they point out that a similar trend in this ratio has been observed in patients with prostatic cancer. Birke and Plantin[10] found normal excretion patterns of individual 17-ketosteroids in rheumatoid arthritis. Norymberski and others[88] claimed an abnormality in the urinary corticosteroid pattern in rheumatoid arthritics. They described a structurally well-defined group designated 17-ketogenic steroids, the

daily excretion of which they found to be 40 per cent below normal values, and to be elevated by corticotropin administration. This steroid group is believed to reflect mainly the adrenal output of hydrocortisone, the principal steroid secreted. Later, however, in a larger series of cases, the average deviation of 17-ketogenic steroid output by rheumatoids was found to be only minus 20 per cent of control values.[4] Dobriner, in 1951, reported the isolation from rheumatoid arthritis urines of a steroid, 17-hydroxypregnenolone, said to be absent from the urine of healthy subjects, but observed to be excreted by subjects with adrenal hyperplasia or tumour. It was concluded that this finding was evidence of adrenocortical dysfunction. However, the same compound was later detected in pregnancy urine, in myeloid leukemia and, in traces, in normal urine.[32,33] So 17-hydroxypregnenolone could no longer be considered a pathologic metabolite, but its excessive excretion in rheumatoid arthritis and the adrenogenital syndrome[3] merited further investigation. Appleby and Norymberski[3] elaborated a method for the group determination of 21-deoxyketol compounds (of which 17-hydroxypregnenolone is a member) involving their selective conversion into 17-ketosteroids. The found no grossly abnormal excretion of this steroid group in rheumatoid arthritics, the average total excretion being less than that of the 17-hydroxypregnenolone originally found by Dobriner in a single case of arthritis. They concluded, therefore, that excessive excretion of 17-hydroxypregnenolone could not be considered an abnormality generally associated with rheumatoid arthritis. A report of deficient aldosterone excretion in rheumatoid arthritis[22] has not been confirmed, and aldosterone itself is not antirheumatic in rheumatoid arthritis.[126]

It seems, therefore, that no specific metabolic defect in steroid excretion has thus far been detected in rheumatoid arthritis, at least not by the techniques used, but it must be admitted that knowledge of the pattern of steroid excretion, even in healthy subjects, is still little more than rudimentary.

Could the abnormality in rheumatoid arthritis lie in a failure of the organism to metabolize endogenous hydrocortisone correctly? This question has been answered by studies using hydrocortisone labeled with C^{14} at the 4-C position.[57,94] No consistent abnormality in the physiologic disposition or metabolic fate of the radioactive hydrocortisone is discernible in subjects with rheumatoid arthritis (or in untreated adrenalectomized subjects), indicating that there is thus no evidence of failure in removal or hepatic conjugation of hydrocortisone.

Although plasma levels of hydrocortisone do not seem abnormal in rheumatoid arthritis, there is some evidence of a disturbance of the normal diurnal rhythm of plasma corticoids in which plasma hydrocortisone normally reaches a peak level around 7 or 8 A. M. and is lowest in the hours after midnight. The peak output in rheumatoid arthritis appears to be consistently decreased,[125,127] and this finding, although probably not specific, corresponds with an alteration in the diurnal pattern of urinary 17-hydroxycorticosteroid and 17-ketosteroid excretion,[60] and accounts for some of the symptoms of the disease.

The presence of endogenous hydrocortisone in rheumatoid synovial fluid was detected by Cope and Sewell[23] and they concluded that there was no barrier at the blood-synovial interface to account for the symptomatology. However,

using a somewhat different technique, Wilson and her co-workers[82,133] failed to find hydrocortisone in significant amounts in synovial fluid of patients with rheumatoid arthritis even when patients were receiving cortisone. But, in view of the widespread nature of the connective tissue reaction in rheumatoid arthritis, it seems unlikely that the question of altered permeability of the synovial barrier to endogenous steroids will be etiologically important.

On the basis of finding an abnormally high urinary excretion of pregnanediol after the administration of progesterone to rheumatoid subjects, Sommerville and others[109] tentatively suggest that an analogous failure of corticosteroid metabolism peripherally in the tissues might be concerned in the production of arthritis. However, there is no knowledge that the enzyme systems concerned in the reduction of progesterone and hydrocortisone are the same, and other workers have failed to confirm these findings.[103] The concept of impaired metabolism of steroids at cellular level in the connective tissues is difficult to explore, but merits consideration if only because the daily requirements of exogenous hormones by the active arthritic are some four to five times as great as the daily output of hydrocortisone by the normal adrenal.[93]

VOL.
5
1957

Physiologically the adrenal is but one link in the neuroendocrine system regulating the homeostatic and defense mechanism of the body, other components being the hypothalamus, the anterior hypophysis, and the autonomic nervous system. Cortical steroid secretion is under the direct control of pituitary corticotropin, the release of which is regulated by the hypothalamus through autonomic neural and humoral "feed back" mechanisms in which blood levels of corticosteroids and epinephrine are concerned. Investigations of pituitary structure, function, and response to adrenergic stimuli are therefore warranted, and Pearse[89] has described specific histochemical changes in the mucoid cells of the anterior pituitary in rheumatoid arthritis similar or identical to those found in Addison's disease, and not occurring in normal subjects or in other disease states. This observation would imply a condition of hypoadrenalism or adrenocortical dysfunction causing secondary pituitary changes, but this implication is not justified until the observation has been confirmed and more is known about the structure and function of the mucoid cells and their relation to the adrenals. So far this observation is unconfirmed.[9] Functionally, the anterior and posterior lobes of the pituitary appear normal in rheumatoid arthritis as far as can be judged by present methods of investigation. The response to epinephrine is unimpaired[116] and the urinary output of follicle-stimulating hormone is normal.[62] No consistent abnormality in production of thyroid-stimulating hormone has been observed.[34]

Although there are no direct observations bearing on a possible relationship of pituitary somatotropic hormone to the pathogenesis of rheumatoid arthritis in man, some recent experimental work is of interest in showing that this particular hormone may be concerned in the causation of a chronic polyarthritis in rats. Briefly, it has been observed that a chronic destructive polyarthritis develops when adrenalectomized-castrated rats are given pituitary growth hormone over a period of months, and that this may also occur in intact animals.[6,99] That the arthritis is not due to nonspecific sensitization to the pituitary extracts used is shown by the equal effectiveness of purified, electrophoretically homogeneous

material. The significance of these observations is at present unclear, and it would be unwise to draw any inferences from them, but pituitary growth hormone appears to be necessary for the formation and maintenance of connective tissues components, especially in cartilage, possibly by virtue of a specific influence on the incorporation of chondroitin sulfate into them.[28,29] It may be of significance that this effect of growth hormone is inhibited by hydrocortisone.

THEORY OF DISORDERED METABOLISM DUE TO HEPATIC DYSFUNCTION

It has long been suspected that liver function may be disordered in rheumatoid arthritis, especially with regard to protein synthesis and carbohydrate metabolism. In recent years the finding of consistently abnormal plasma protein patterns and abnormalities in the so-called "liver function" flocculation tests associated with hyperglobulinemia has provoked a large number of investigations into various aspects of hepatic function in rheumatoid arthritis, often with conflicting or contradictory results. But more solid evidence of inconsistent and mild, yet definite, impairment of some hepatic processes is now becoming apparent.

Structurally, the liver shows no specific histologic abnormality,[7,72,86] and its ability to excrete bile pigments (a crude test of hepatocellular function) is unquestionably normal.[25,72,103] So also is the production of the enzymes, alkaline phosphatase, and cholinesterase.[53,72,112,123] Most observers find blood levels of cholesterol to be within normal limits in rheumatoid arthritis,[11,103] and blood and urinary creatine levels are also reported as being normal.[27] A study of the urinary output of coproporphyrin claims to show the presence of mild hepatic impairment in one-third of the cases tested.[25] Prothrombin synthesis has also been investigated, and is said to be moderately reduced in 20 per cent of cases.[72]

Carbohydrate intolerance was first suspected in rheumatoid arthritics because when given glucose orally or intravenously their blood sugar curves sometimes showed a slow return to fasting levels.[40,91,131] Elevated sugar tolerance curves in arterial blood, with normal arteriovenous differences in simultaneous venous samples, were also taken to indicate decreased hepatic glycogenolysis.[2] But apparent intolerance to carbohydrate cannot properly be evaluated without considering the general nutritional status and prior levels of carbohydrate intake of the subjects, and these factors were generally neglected in early studies. In addition, glucose metabolism is not entirely an hepatic function. More accurate information can be gained from studying tolerance to fructose, a sugar not normally present in the blood, which is almost exclusively metabolized by the liver, and for which specific methods of determination are available. In a thoughtful, controlled study of fructose tolerance in rheumatoid arthritics, some 60 per cent were found to have abnormal blood curves, and this seems to provide evidence of mild impairment of hepatic glycogenolysis in this disease.[103]

A theory that the cause of rheumatoid arthritis lies in a reduced hepatic capacity to convert carbohydrate is based on the observation in this disease of subnormal blood citric acid levels and elevated pyruvate levels, together with hyperglobulinemia.[18,79] Although the proponents of this theory claim that the administration of adenosine triphosphate, given to stimulate carbohydrate conversion, is beneficial in rheumatoid arthritis, other investigators have found it to be of no value.[49,129]

The ability of the liver to conjugate benzoic acid with glycine in hippurate synthesis has been investigated in rheumatoid arthritis, and although in some studies it has been found deficient in varying proportions of cases,[79,103] other investigators have found no such abnormality.[59,73]

The capacity of rheumatoid subjects to acetylate *p*-aminobenzoic acid and sulfadiazine has been investigated and found to be normal, although this may not exclude hepatic disease.[45,68]

The excretory capacity of the liver was studied using the dye azorubin S given intraduodenally, and was found in one study to be impaired in some 55 per cent of patients.[98] But a more reliable and sensitive test of hepatocellular dysfunction, when correctly performed, is hepatic excretion of Bromsulphalein (BSP). BSP excretion was found to be normal in two studies[73,101] but the technique used has been criticized, and significant but small amounts of dye retention have been found by other workers in from 20 to 50 per cent of the cases.[25,72,86] BSP clearance is dependent not only on the ability of the liver to concentrate and then excrete the dye, but also on the rate of hepatic blood flow, and this factor has not received independent study.

VOL.
5
1957

Because of the marked general tissue wasting, negative nitrogen balance, and hypoalbuminemia which rheumatoid patients frequently develop, the possibility of an intrinsic disturbance of protein metabolism has received attention. Albumin is synthesized in the liver. Studies of nitrogen balance on changing from a low to a high protein intake have shown no pattern of nitrogen retention that could be correlated with the severity or duration of the arthritis, the greatest increments in retained nitrogen occurring in those patients most underweight.[102] Determinations of the urinary excretion and plasma levels of total and individual amino acids (including hydroxyproline and glycine, which together comprise one-third of the amino acid residues of collagen) show no striking deviation from the normal.[14,15,103,136] Infused serum albumin and gamma globulin disappear from the blood stream more rapidly in rheumatoid arthritics than in normal subjects, but this may be due to chronic malnutrition associated with the negative nitrogen balance, or possibly to a specific immunologic response in this disease.[120]

The most consistent evidence for a belief of deranged liver function in rheumatoid arthritis is the altered plasma protein electrophoretic pattern and concurrent abnormalities in serum flocculation tests related to hyperglobulinemia. The tests most frequently positive in rheumatoid arthritis are the colloidal gold, cephalin-cholesterol flocculation, thymol turbidity, and zinc sulfate reactions[5,19,103]; the colloidal gold test is the most frequently abnormal. The plasma protein changes most commonly encountered consist of depression of the albumin and elevation of the globulin and fibrinogen peaks.[5,86,105,114] The latter is largely responsible for changes in the erythrocyte sedimentation rate. The major increase in the globulin is in the euglobulin fraction,[26] more specificially, the alpha-2 and gamma globulin peaks, resulting in a depressed albumin alpha-2 globulin ratio. Similar electrophoretic patterns are found in rheumatic fever and, as they revert to normal when the disease remits, can be used in the assessment of disease activity. In both diseases there is also an increase in protein-bound polysaccharide, particularly in the elevated alpha-2 fraction.[69,80]

Finally, the ability of the liver to conjugate hydroxycorticosteroids in rheumatoid arthritis must be considered, as 95 per cent or more of administered hydrocortisone is excreted in conjugated form. The normal plasma levels of hydroxycorticosteroids found in rheumatoid arthritis would not necessarily exclude impairment of hepatic excretion, as has been demonstrated in both acute and chronic liver damage.[16,117] However, studies with intravenously administered, isotopically labeled hydrocortisone have shown no inability of the rheumatoid subject to remove it from the blood stream or to excrete it in conjugated form.[94]

It is difficult to interpret the varied and sometimes contradictory data concerning liver function in rheumatoid arthritis in etiologic terms. It is improbable that the plasma protein changes found by chemical and electrophoretic studies, or indirectly by abnormalities of flocculation and turbidity tests, reflect disordered hepatic function; they are known to occur in conditions without liver damage. The cause of the hyperfibrinogenemia is not known, but it is not a feature of liver damage. The hyperglobulinemia, which is the most consistent finding, might be an immunologic rather than a hepatotoxic reaction. The most that can be said is that some 20 to 33 per cent of patients have evidence of some minor hepatic dysfunction at some time, but there is no evidence of any primary dysfunction that could be etiologically related to rheumatoid arthritis.

THEORY OF HYPERSENSITIVITY

The theory of allergy, or acquired hypersensitivity to a foreign protein, as the pathogenetic basis of rheumatoid arthritis has become increasingly prominent in the past twenty years, and to many observers a state of sustained allergic reaction in the tissues offers the only satisfactory explanation of this chronic, often lifelong, inflammatory process, involving connective tissues in almost all sites of the body. The granulomatous nature of the tissue reaction which, although characteristic and generally diagnostic is, nevertheless, nonspecific, is an added appeal to the devotees of this concept. If the process is an allergic one, it could be either of the immediate anaphylactic or delayed tuberculin type, and studies of experimentally induced hypersensitivity states of both types in laboratory animals appear to have some bearing on the mechanisms that might be involved. If rheumatoid inflammation is a reaction to antigen-antibody union at selected sites in the connective tissues, the supply of antigen must necessarily be continuous or the reaction must in some way be self-perpetuating. Rheumatic fever, generally accepted as an hyperimmune response to unknown antigens in beta hemolytic streptococci, is a self-limiting disease, and its reactivation is dependent on streptococcal reinfection. The same is true of acute glomerulonephritis. As there is no evidence of bacterial infection in rheumatoid arthritis, this difficulty regarding the source of the supposed antigen may theoretically be overcome by the supposition of an autogenous supply of antigen, a component of the host's own connective tissues rendered antigenic, either as a full antigen or a hapten, by some alteration in its environment. This theory of autoimmunization, although attractive, is as yet unproved in any disease other than some of the acquired hemolytic anemias.

Probably the first serious contribution to the hypersensitivity concept was the work of Klinge who, in 1933, postulated hypersensitivity as the cause of rheumatic fever and suggested a similar etiology for rheumatoid arthritis. In the next few years there were many clinical claims to have demonstrated an allergic factor in rheumatoid arthritis, mostly to foodstuff allergens, but the evidence on which these claims were based was tenuous, usually involving uncontrolled skin-testing of selected patients, and, besides being inferential only, would not now stand up to critical scrutiny.

The presence in rheumatoid sera of agglutinins for streptococci provided material for a belief that allergy to these organisms was the cause of the disease. But it is now known that the factor causing streptococcal agglutination is not specific for this or any other organism, and although it cannot be said that it is not an antibody of some sort, it can be said with certainty that its presence is not an immune response to streptococcal infection. The mechanism of streptococcal aggulutination in rheumatoid arthritis is best explained as an interaction between an unknown serum globulin component and a reactant in the gamma globulin fraction, the role of streptococci being the nonimmunologic one of serving as a carrier for the gamma globulin reactant and an indicator of a precipitin reaction between the two globulin factors.

Clinical observations of its natural history having yielded no information as to the possible role played by hypersensitivity in the causation of rheumatoid arthritis, the evidence suggesting that it might do so is as yet indirect, based on observations of nosologically similar connective tissue disorders in man and on studies of experimentally induced hypersensitivity states in animals.

This evidence has been well stated by Rich,[100] many of the observations being his own. Rich's views are largely based on the observation of the basic similarity of the connective tissue lesions of a group of diseases comprising rheumatoid arthritis, disseminated lupus erythematous, polyarteritis nodosa, rheumatic fever, serum sickness, anaphylactoid purpura, and acute glomerulonephritis, and on the further observation, drawn from a large volume of experimental studies, that histologically identical focal collagen and necrotizing vascular lesions can be caused in animals by immunization with foreign proteins. Rich believes the anaphylactic type of hypersensitivity to foreign antigens to be the cause of the diseases in this nosologic group, and stresses also the close similarity between the clinicopathologic manifestations of these diseases with those of the experimental anaphylactic state. Although the mechanism of tissue injury in all these examples is the hyperimmune state, the responsible etiologic agents are assumed to be diverse, bacterial and nonbacterial, protein, and hapten. Examples of agents known to be antigenically-active in disease processes in man include foreign proteins, iodine, and sulfonamides in polyarteritis nodosa; hemolytic streptococcal products in rheumatic fever, acute glomerulonephritis, and anaphylactoid purpura; and drugs such as Sedormid in acquired thrombocytopenic purpura.[1]

The lesions caused by intravenous injections of foreign proteins in animals in the heart, arteries, kidneys, and joints closely resemble those found in some connective tissue disorders, the analogy being perhaps closest in rheumatic fever and acute nephritis, and are accompanied by serologic evidence of antibody

VOL.
5
1957

formation.[54] Homologous tissue transplants provoke the same histologic and immunologic responses. Studies of the articular lesions of induced delayed-type (tuberculin) hypersensitivity in animals shows them to bear a stronger resemblance to rheumatoid arthritis than those of immediate-type (anaphylactic) hypersensitivity.[13,90]

The morphologic similarity of the visceral lesions of human subjects dying of drug sensitivity with those of the experimentally hypersensitive animal on the one hand, and the lesions of the connective tissue diseases on the other, is sufficiently striking to suggest a common pathogenesis for them all,[85] although not necessarily a common etiology.

The search for an exogenous antigen in rheumatoid arthritis responsible for the hypothesized hypersensitivity state has so far proved unrewarding. Human pleuropneumonia-like organisms in the L form offer a persistent source of living antigen, invisible in tissues and cells and not demonstrable by routine methods, which would theoretically satisfy the criteria for such an antigen.[132] In addition, they can cause chronic polyarthritis in mice.[39,104] However, L organisms cannot be isolated from the blood, tissues, or synovial fluid in rheumatoid arthritis,[43,97] although claims for the detection of serologic agglutinins to them have been made in cases of Reiter's syndrome.[31,123]

"Hypersensitive" types of cutaneous responses to streptococcal vaccines have been noted in conditions of proved streptococcal allergy (rheumatic fever, erythema nodosum) and also in some cases of rheumatoid arthritis, but the lesions produced more closely resemble those of the Arthus type of reaction and serum sickness, and do not justify any conclusive inferences with regard to streptococcal allergy in rheumatoid arthritis.[64]

The hyperimmune state may be provoked not only by exogenous allergens but also by autoimmunization to components of body tissues rendered antigenic by contact with bacteria or bacterial products, and provoking the formation of tissue-specific antibodies. In the experimental animal, immunization with homologous tissues conjugated with streptococcal vaccine results in the formation of specifically active autoantibodies to heart, connective tissue, and muscle, demonstrable in vivo, and pathologic lesions in the same organs broadly resembling those of rheumatic fever.[21]

But hypotheses of autoantibody formation to human tissue components are difficult to substantiate. The hyperglobulinemia of rheumatoid arthritis has been suggested as evidence of a hyperimmune response of this nature,[103,124] but rheumatoid gamma globulin (Cohn fraction II) isotopically labeled with I^{131} shows no special affinity for equilibration with either normal or rheumatoid joint tissue, in vitro or in vivo.[120] Attempts to identify antibodies in rheumatoid sera to antigen prepared from normal and pathologic joint tissues have been unsuccessful,[71] and skin-testing with filtrates of rheumatoid synovium, nodules, and synovial fluid fails to demonstrate an immune response in rheumatoid subjects.[80]

Experimentally, efforts to produce arthritis in animals by immunization with homologous joint and other tissues, with or without the addition of streptococcal vaccine, have failed to cause arthritis or antibody formation.[83] The

Masugi type of experimental nephritis has been used as a model in an effort to produce a synovotoxic arthritis, but both rabbit and guinea pig anti-guinea-pig-joint sera, labeled with I^{131}, failed to localize in the joints when injected into normal guinea pigs, or to cause synovial inflammation.[38]

One of the stumbling blocks to the autosensitization concept in rheumatoid arthritis is the nonantigenicity of known isolated connective-tissue components, with the exception of reticulin.[24] Purified collagen and gelatin are nonantigenic,[81,110] and cannot be rendered so by coupling with diazotized sulfanilic acid or human serum globulin.[122] The acid-soluble fraction of rattail collagen is mildly antigenic[128] but this particular type of collagen is not found in human connective tissues. Antibodies to human collagen, of complement-fixing or precipitating type, cannot be found in the sera of patients with rheumatoid arthritis or other connective tissue diseases.[122] Of the connective tissue mucopolysaccharides, hyaluronic acid is nonantigenic alone, after conjugation with horse serum albumin, or even when present in the capsules of virulent strains of streptococci.[63,84] Another prominent connective tissue mucopolysaccharide, chondroitin sulfate, is also nonantigenic, but it has been claimed that it can be made so in rabbits by conjugation with group A hemolytic streptococcal vaccine. Chondroitin sulfate-treated vaccine is said to give rise not only to sera precipitating specifically with this mucopolysaccharide, but also to polyarthritis in rabbits immunized with it.[47] However, there are grounds for believing that the antigenic stimulant lies not in the chondroitin sulfate itself, but in a protein connective tissue component contaminating it.[12] Nevertheless, some vegetable and synthetic polysaccharides, themselves not antigenic in the rabbit, do acquire specific antigenicity after adsorption onto hemolytic streptococci,[48] and this still remains a possible mechanism of autosensitization.

The therapeutic efficacy of steroid hormones in rheumatoid arthritis has been interpreted as a substantiation of the allergic origin of the disease.[51] The case put forward by the proponents of this theory is based on the known action of steroids in causing inhibition of cellular mitosis and also of depressing homologous and heterologous immunity to tumor growth in the mouse. Depression of host immune responses is said to be due to inhibition of mitosis of the reticuloendothelial cells, with resultant abolition of antibody formation and consequently of the allergic inflammatory response. Such a mechanism could account for the nonspecific nature of the antiphlogistic action of steroid hormones, and possibly also for their uricosuric and nitrogen-retaining effects, because of impaired nucleoprotein synthesis.

This suggested theory of the antiallergic action of steroid hormones in rheumatoid arthritis is not supported by parallel investigations. The tissue response in known bacterial allergies, such as tuberculin hypersensitivity in guinea pigs, is strongly inhibited by cortisone and corticotropin.[74] If there is an analogy between the delayed type of allergy and the tissue reaction in rheumatoid arthritis, factors affecting the former might also be expected to influence the latter.[75,76] But glucose-one-phosphate, lysergic acid-diethylamide, and ascorbic acid saturation, all of which suppress or diminish experimental tuberculin hypersensitivity, do not influence either the disease process or the reaction to

purified protein derivative of tuberculin in patients with rheumatoid arthritis.[78] Although these experiments fail to support an analogy between experimental tuberculin-type hypersensitivity and the rheumatoid state, they also do not refute it.

THE RELATION OF SEROLOGIC AGGLUTINATION PHENOMENA TO THE CAUSATION OF RHEUMATOID ARTHRITIS

The sensitized sheep cell agglutination test, its modifications, and subsequent development are discussed elsewhere in this issue, and have also been dealt with at length in another publication,[35] but it is germane to the problem of the pathogenesis of rheumatoid arthritis to discuss here some possible implications of this perplexing phenomenon.

That the reaction to this test is of fundamental importance cannot be doubted. Its specificity for the adult and juvenile forms of rheumatoid arthritis, its absence in the pathologically related conditions, ankylosing spondylitis and psoriatic arthritis, and its failure to be influenced by remissions of the disease all point to some pathogenetic relationship and exclude a nonspecific inflammatory causation.

Chemical identification of the rheumatoid agglutinating factor (AF) is proving very difficult despite the use of diverse chemical and electrophoretic techniques of plasma fractionation. AF is nondialysable and thermostable, has been variously located in the beta and gamma globulin fractions of serum, and has been associated with both beta-lipoprotein,[56] and beta-glycoprotein.[107,119] Very recently Greenbury[52] succeeded in eluting the factor in concentrated form from agglutinated erythrocytes and the use of his technique may help to clarify its chemical and immunologic structure. Previous attempts to recover the factor from serum by adsorption on sensitized cells, barium sulfate, asbestos, and paper had met with no success.

Rheumatoid AF shows no specificity for the system used as substrate, either regarding the source of the cells agglutinated or the source of the sensitizing amboceptor, and even the patient's own washed erythrocytes can be used if sensitized with homologous antibody.[46] Nevertheless, AF does not enhance agglutination by normal human or infectious mononucleosis sera, or by anti-Rh sera against Rh-positive cells, so it is not an enhancer of nonspecific agglutination. Its action is augmented by nonimmune sera and pooled human plasma,[95,134] another feature suggestive of an immune antigen-antibody reaction.

The lack of immunologic specificity of the reaction leads to the conclusion that in the sensitized erythrocyte systems generally used, the erythrocytes are not the source of antigen, and this was proved by Heller and others[55] who demonstrated that tannic acid-coated (and therefore immunologically inert) erythrocytes are agglutinated by active rheumatoid sera when coated with human serum Cohn fraction II (electrophoretically, gamma globulin). Washed and amboceptor-sensitized erythrocyte stroma are also capable of being agglutinated.[115] Erythrocytes can, in fact, be eliminated from the system entirely, as the factor is also active in nonagglutinating systems and can be adsorbed on the immune precipitates from the antisera of rabbits immunized with crystalline egg albumin or conalbumin, although it cannot be adsorbed by barium sulfate.[118,119]

Other immune systems known to detect agglutination are *Brucella abortus* and human antibrucella serum,[41] pneumococcal polysaccharide-coated erythrocytes sensitized with pneumococcal antiserum, and A-substance-coated human group A cells sensitized with anti-A antibody. However, agglutination does not occur with fowl cells sensitized with incomplete antifowl cell antibody, or with sheep cells sensitized with anti-Forssman antibody.[52]

The first conclusion to be drawn from these observations is that the function of erythrocytes in the test is that of an immunologically inert carrier of an active fraction contained in the sensitizing antiserum, and an indicator of the reaction between it and the AF. Support for this conclusion is the demonstration that polystyrene latex particles coated with pooled human gamma globulin will serve as a carrier mechanism.[96] Furthermore, active rheumatoid sera will cause a precipitin reaction with pooled human serum fraction II, and the reaction is inhibited by an excess of fraction II. The reacting portion of the fraction II (F II) is only a part of the total gamma globulin.[37] A second conclusion which might be drawn, therefore, is that if AF is really an antibody in an immune reaction, as these findings seem to suggest, the antigen concerned must necessarily be a gamma globulin constituent of normal human serum F II, and also of a wide range of antisera, without species-specificity.

VOL.
5
1957

Further recent observations of some significance concern reversal of the agglutination by AF of pneumococcal polysaccharide-coated erythrocytes sensitized with antipneumococcal serum, by an excess of the pneumococcal polysaccharide, and also of the analogous reaction with human A-substance and anti-A antiserum by excess A-substance.[52] When reversal occurs, free AF is liberated in the supernate. Note that in these examples reversal or inhibition occurs only with the antigen specific for the amboceptor used. (Ziff and others[135] were able to inhibit the sensitized sheep cell test with pooled human gamma globulin not only in vitro, but also in vivo.)

The most likely explanation of these reversal-inhibition phenomena is competition between AF and excess antigen for union with the divalent sensitizing amboceptor on the carrier, and some confirmation of this is found in Greenbury's failure, with active sera, to cause agglutination of cells sensitized with incomplete (univalent) antibody. But as he points out, there is no explanation of why AF attaches itself only to antibody combined with its antigen.

A further complication in the elucidation of the agglutination mechanism is the observation of Vaughan[119] that active sera, completely absorbed by immune precipitates of all agglutinating activity for sensitized erythrocytes, still retain the power of agglutinating tanned, F II-coated cells. Does this imply two separate agglutinating factors? (Lospalluto and Ziff,[77] in the most intensive chemical purification of AF yet achieved, find in their 500-fold-purified material two components, both with slow mobilities in the gamma globulin range), or does it mean a single agglutinin with cross-reacting specificity?

A third possibility is that AF may be a complement, but there is no definitive evidence for this at the present time. Agglutinating activity has been related to an increased hemolytic titer of the fourth component of complement,[50,61] but this finding is not generally accepted[8,17] and Japanese workers believe agglutinating activity can be related to the first component of complement.[106]

Vaughan[119] feels that the failure of AF to be adsorbed on the immune precipitates from the antisera of guinea pigs immunized with crystalline egg albumin, whereas it is adsorbed by the same system prepared in rabbits, is evidence against its being hemolytic complement, this system being particularly active in complement fixation. Serum levels of hemolytic complement are said to be elevated in some cases of rheumatoid arthritis[121,130] but there is considerable dispute about this,[66] and in any case positive agglutination tests cannot be correlated with serum complement levels.

One further point deserves mention in elucidating the complex mechanics of this agglutination phenomenon, and that is that an inhibitor to agglutination, already mentioned as being in Cohn's fraction II of normal sera, and active both in vitro and in vivo[55,135] is absent in rheumatoid arthritis, but not in ankylosing spondylitis, psoriatic arthritis, or related disorders, and its absence is of diagnostic significance in this disease.[135]

The implications of all these observations are far from clear, and too much speculation would be unwise. AF has many features of an antibody to an antigen normally present in serum globulin and almost all antisera. It is probably not hemolytic complement, and may itself by immunologically complex and not a single antibody. Its action is inhibited or reversed by excess of its substrate and an inhibitor to it is normally present in gamma globulin, but is absent in rheumatoid arthritis. If it is an antibody to a connective tissue component rendered antigenic by conjugation with a constituent of plasma globulin, why is it not adsorbed by globulin-sensitized erythrocytes, why do positive sera not give a positive antihuman globulin test; and why is its titer not reduced by steroids?[113]

None of these questions have been answered. Heller believed AF to be a true antibody, and the globulin reactant used to elicit the reaction does so because of its structural affinity to an original sensitizing antigen—in other words it behaves as a sort of false antigen. But the clue to the pathogenesis of rheumatoid arthritis may lie in the absence, in this disease, of the agglutination inhibitor normally present.

CONCLUSIONS

Every theory of the cause of rheumatoid arthritis yet propounded lacks sufficient scientific evidence to make it generally acceptable, and the theories discussed here are no exception. And yet, in our present state of knowledge, they seem to be the concepts from which the answer will eventually most likely be derived. It seems clear that the answer to the problem can come only from combined research in the fields of clinical science—the planned study of disease and its phenomena in people who are ill; and basic science—the study of the structure and function of the fundamental connective tissues themselves.

REFERENCES

1. Ackroyd, J. F.: Cause of Thrombocytopenia in Sedormid Purpura, Clin. Sc. **8**:269, 1949.
2. Andrews, K. R., and Muether, R. O.: Effect of Diet on Arterial and Venous Glucose Tolerance Curves in Rheumatoid Arthritis, J. Lab. & Clin. Med. **26**:675, 1940.
3. Appleby, J. I., and Norymberski, J. K.: Indirect Analysis of Corticosteroids. II. The Determination and Identification of Urinary 17-hydroxy-20-oxosteroids Unsubstituted at C_{21}, Biochem. J. **60**:460, 1955.

VOL.
5
1957

4. Appleby, J. I., and Norymberski, J. K.: Urinary Excretion of 17-hydroxy-20-oxosteroids in Normal Health and in Rheumatoid Arthritis, Ann. Rheumat. Dis. **14**:172, 1955.
5. Archer, B. A.: Liver Function Tests in Non-specific Arthritis With Special Reference to Hyperglobulinaemia, Ann. Int. Med. **34**:1173, 1951.
6. Asling, C. W., Simpson, M. E., Moon, H. D., Li, C. H., and Evans, H. M.: Growth-hormone-induced Osteoarthropathy, Ann. Rheumat. Dis. **13**:364, 1954.
7. Bagenstoss, A. H., and Rosenberg, E. F.: Visceral Lesions Associated With Chronic Infections (Rheumatoid) Arthritis, Arch. Path. **35**:503, 1943.
8. Ball, J.: Agglutination Tests for Rheumatoid Arthritis, Lancet **1**:614, 1952.
9. Bennett, W. A.: Histopathological Alteration of Adrenal and Anterior Pituitary Glands in Patients Treated With Cortisone, J. Bone & Joint Surg. **36A**:867, 1954.
10. Birke, G., and Plantin, L. O.: Studies on Urinary 17-Ketosteroids, Acta med. scandinav. (Suppl. 291) **148**:1, 1954.
11. Block, W. D., Buchanan, O. H., and Freyberg, R. H.: Serum Lipids in Patients With Rheumatoid Arthritis and in Patients With Obstructive Jaundice; Comparative Study, Arch. Int. Med. **68**:18, 1941.
12. Boake, W. C., and Muir, H.: Non-antigenicity of Chondroitin Sulphate, Lancet **2**:1222, 1955.
13. Bocking, D., and Brien, F. S.: Comparative Pathology of Experimental Arthritis Due to Formalin, Blood, Immediate and Delayed-Type Hypersensitivity Reactions, Ann. Rheumat. Dis. **14**:99, 1954.
14. Borden, A. L., Wallraff, E. B., Brodie, E. C., Holbrook, W. P., Hill, D. F., Stephens, C. A. L., Kent, L. J., and Kammerer, A. R.: Plasma Levels of Free Amino Acids in Normal Subjects Compared With Patients With Rheumatoid Arthritis, Proc. Soc. Exper. Biol. **75**:28, 1950.
15. Brodie, E. C., Wallraff, E. B., Borden, A. L., Holbrook, W. P., Stephens, C. A. L., Hill, D. F., Kent, L. J., and Kammerer, A. R.: Urinary Excretion of Certain Amino Acids During ACTH and Cortisone Treatment of Rheumatoid Arthritis, Proc. Soc. Exper. Biol. **75**:285, 1950.
16. Brown, H., Willardson, D. G., Samuels, L. T., and Tyler, F. H.: 17-Hydroxycorticosteroid Metabolism in Liver Disease, J. Clin. Invest. **33**:1524, 1954.
17. Bunim, J. J.: In discussion on: Haemagglutination Test for Rheumatoid Arthritis: A Clinical Analysis, Ann. Rheumat. Dis. **13**:321, 1953.
18. Carlstrom, B., and Lovgren, O.: Treatment of Rheumatoid Arthritis With Adenosinetriphosphate, Ann. Rheumat. Dis. **8**:293, 1949.
19. Carter, A. B., and MacLagen, N. F.: Some Observations on Liver Function Tests in Diseases Not Primarily Hepatic, Brit. M. J. **2**:80, 1946.
20. Caughey, J. E., and McCoy, J. E.: Addison's Disease With Associated Polyarthritis. An Aetiological Study of the Arthritis Syndrome, Brit. M. J. **2**:1189, 1951.
21. Cavelti, P. A.: Studies on the Pathogenesis of Rheumatic Fever. I. Experimental Production of Autoantibodies to Heart, Skeletal Muscle and Connective Tissue. II. Cardiac Lesions Produced in Rats by Means of Autoantibodies to Heart and Connective Tissue, Arch. Path. **44**:1, 1947.
22. Cope, C. L., and Garcia-Llaurado, J.: Occurrence of Electrocortin in Human Urine, Brit. M. J. **1**:1290, 1954.
23. Cope, C. L., and Sewell, C. E.: The Presence of Natural Hydrocortisone in Synovial Fluid, Ann. Rheumat. Dis. **15**:392, 1956.
24. Cruickshank, B., and Hill, A. G. S.: The Histochemical Identification of a Connective Tissue Antigen in the Rat, J. Path. & Bact. **66**:283, 1953.
25. Darby, P. W.: Liver Function Tests in Rheumatoid Arthritis, J. Clin. Path. **9**:153, 1956.
26. Davis, J. S.: Protein Studies in Atrophic (Rheumatoid) and Hypertrophic Arthritis, J. Lab. & Clin. Med. **21**:478, 1935.
27. Dawson, J. E., and Salt, H. B.: Creatine Metabolism in Arthritis, Ann. Rheumat. Dis. **11**:23, 1952.
28. Denko, C. W., Bergenstal, D. M., and Kenyon, A. T.: Effect of Cortisone on Radioactive Sulphur Uptake in Cartilage, Ann. Rheumat. Dis. **14**:94, 1954.
29. Denko, C. W., Kenyon, A. T., and Bergenstal, D.: Effect of Hypophysectomy and Growth Hormone on Radioactive Sulphur Uptake in Cartilage, Ann. Rheumat. Dis. **13**:360, 1954.
30. Devis, R.: Chemical Methods and Clinical Applications of Chromatographic Fractionation of Urinary Steroids, Ann. endocrinol. **12**:451, 1951.
31. Dienes, L., Berg, R. L., and Weinberger, H. J.: Further Observations on the Incidence and Significance of Pleuropneumonia-like Organisms, Ann. Rheumat. Dis. **7**:259, 1948.
32. Dobriner, K.: Adrenal Function in Rheumatoid Arthritis, Bull. Rheumat. Dis. **2**:5, 1951.
33. Dobriner, K., Kappas, A., and Gallagher, T. F.: Studies in Steroid Metabolism. XXVI. Steroid Isolation Studies in Human Leukemia, J. Clin. Invest. **33**:1481, 1954.
34. Dresner, E.: Aetiology and Pathogenesis of Rheumatoid Arthritis, Am. J. Med. **18**:74, 1955.

35. Dresner, E.: Serological Agglutination and Precipitin Mechanisms in Rheumatoid Arthritis, Postgrad. M. J. (In press.) 1957.
36. Ellman, P., and Cudkowicz, L.: Comparative Effects of Cortisone, ACTH and DOCA in a Case of Rheumatoid Arthritis With Addison's Disease, Ann. Rheumat. Dis. **11**:225, 1952.
37. Epstein, W., Johnson, A. M., and Ragan, C.: Precipitin Reaction Between Human Gamma Globulin and the Serum of Patients Having Rheumatoid Arthritis, Bull. Rheumat. Dis. **7**:114, 1956.
38. Favour, C. B., Goldthwaite, J. C., and Bayles, T. B.: Attempt to Produce Experimental Arthritis With Synovotoxic Antiserum Tagged With I^{131}, Ann. Rheumat. Dis. **13**:369, 1954.
39. Findlay, G. M., MacKenzie, R. D., and MacCallum, F. O.: Chemotherapeutic Experiments on Pleuropneumonia-like Organisms in Rodents, Brit. J. Exper. Path. **21**:13, 1940.
40. Flynn, J. E., and Irish, O. J.: Blood Sugar Level Following Intravenous Glucose in Rheumatoid Arthritis, Science **104**:344, 1946.
41. Foz, A., Batalla, E., and Espacio, L.: Autoantibodies in Rheumatoid Arthritis. A Simple Method of Demonstration With Possible Diagnostic Application, Rev. diagn. biol. (Madr.) **3**:460, 1954.
42. Fredell, E. W., Johnson, H. P., Krupp, M. A., Engelman, E. P., and McGrath, A. K.: Adrenocortical Function During Long-Term Cortisone Therapy, A. M. A. Arch. Int. Med. **95**:411, 1955.
43. Freyberg, R. H., Block, W. D., and Fromer, M. F.: Study of Sulphur Metabolism and the Effect of Sulphur Administration in Chronic Arthritis, J. Clin. Invest. **19**:423, 1940.
44. Gennes, L. de, Bricaire, H., and Villiaumey, J.: Clinical Aspects of the Arthritis Provoked by Deoxycortone, Rev. Rheumat. **22**:1, 1955.
45. Gershberg, H., and Kuhl, W. J.: Acetylation Studies in Human Subjects With Metabolic Disorders, J. Clin. Invest. **29**:1625, 1950.
46. Gibson, H. J., and Ling, N. R.: Modified Waaler-Rose Reaction Employing Sensitized Human Cells, Ann. Rheumat. Dis. **15**:246, 1956.
47. Glynn, L. E., and Holborrow, E. J.: Conversion of Tissue Polysaccharides to Autoantigens by Group A Beta-Haemolytic Streptococci, Lancet **2**:449, 1952.
48. Glynn, L. E., and Holborrow, E. J.: Production of Complete Antigens From Polysaccharide Haptenes by Streptococci and Other Organisms, J. Path. & Bact. **64**:775, 1952.
49. Godfrey, L.: Adenosine Triphosphate Trial in the Treatment of Rheumatoid Arthritis, J.A.M.A. **145**:318, 1951.
50. Gorrill, R. H., and Hobson, D.: The Agglutinating Property of Complement, J. Path. & Bact. **64**:257, 1952.
51. Green, H. N.: Suggested Mode of Action of Corticotrophin in Rheumatoid Arthritis and the Allergic State, Brit. M. J. **1**:1165, 1950.
52. Greenbury, C. L.: Elution of the Rheumatoid Arthritis Factor From Red Cell Agglutinates, Lancet **2**:644, 1956.
53. Grob, D., Lilienthal, J. L., Harvey, A. M., and Jones, B. F.: Administration of Di-isopropyl Fluorophosphate (DFP) to Man: Effect on Plasma and Erythrocyte Cholinesterase, etc., Bull. Johns Hopkins Hosp. **81**:217, 1947.
54. Hawn, C. Z., and Janeway, C. A.: Histological and Serological Sequences in Experimental Hypersensitivity, J. Exper. Med. **85**:571, 1947.
55. Heller, G., Jacobson, A. S., Kolodny, M. H., and Kammerer, W. H.: The Haemagglutination Test for Rheumatoid Arthritis. II. The Influence of Human Plasma Fraction II (Gamma Globulin) on the Reaction, J. Immunol. **72**:66, 1954.
56. Heller, G., Kolodny, M. H., LePow, I. H., Jacobson, A. S., Rivera, M. E., and Marks, G. H.: Haemagglutination Test for Rheumatoid Arthritis. IV. Characterization of the Rheumatoid Agglutinating Factors by Analysis of Serum Fractions Prepared by Ethanol Fractionation, J. Immunol. **74**:340, 1955.
57. Hellman, L., Bradlow, H. L., Adesman, J., Fukusaima, D. K., Kulp, J. L., and Gallagher, T. F.: The Fate of Hydrocortisone-C^{14} in Man, J. Clin. Invest. **33**:1156, 1954.
58. Hench, P. S., Kendall, E. C., Slocumb, C. H., and Polley, H. F.: Effects of Cortisone Acetate and Pituitary ACTH on Rheumatoid Arthritis, Rheumatic Fever and Certain Other Conditions; A Study in Clinical Physiology, Arch. Int. Med. **85**:545, 1950.
59. Hepburn, J. S., Warter, P. J., and Rosenstein, G.: Liver Function in Arthritis Measured by the Hippuric Acid Test, Rev. Gastroenterol. **10**:126, 1943.
60. Hill, S. R., Holley, H. L., Starnes, R. R., and Hibbett, L. L.: Studies on the Diurnal Pattern and Ratio of Urinary 17-Hydroxycorticosteroid and 17-Ketosteroid Excretion in Patients With Rheumatoid Arthritis and Non-rheumatic Chronic Diseases, Ann. Rheumat. Dis. **15**:69, 1955.
61. Hobson, D., and Borrill, R. H.: Agglutination Test for Rheumatoid Arthritis, Lancet **1**:389, 1952.

62. Howard, R. P., Venning, E. H., and Fisk, G. H.: Rheumatoid Arthritis. II. Studies of Adrenocortical and hypophyseal Function and the Effects Thereon of Testosterone and Pregnenolone Therapy, Canad. M.A.J. **63**:340, 1950.
63. Humphrey, J. A.: Antigenic Properties of Hyaluronic Acid, Biochem. J. **37**:460, 1943.
64. Humphrey, J. H., and Pagel, W.: Tissue Response of Heat-killed Streptococci in the Skin of Normal Subjects and in Persons With Rheumatic Fever, Rheumatoid Arthritis, Subacute Bacterial Endocarditis and Erythema Nodosum, Brit. J. Exper. Path. **30**:282, 1949.
65. Kalliomaki, J. L., and Kasanen, A.: Peroral Potassium Tolerance Test in Peptic Ulcer, Rheumatoid Arthritis, and Arterial Hypertension, Acta med. scandinav. **155**:307, 1956.
66. Kellett, C. E.: Complementary Activity of the Blood in Rheumatism and Certain Allied Disorders, Ann. Rheumat. Dis. **13**:211, 1954.
67. Kellie, A. E., and Wade, A. P.: Urinary Steroid Excretion in Rheumatoid Arthritis, Brit. M. J. **2**:594, 1953.
68. Kuhl, W. J., Gershberg, H., and Ralli, E. P.: Acetylation Studies in Patients With Rheumatoid Arthritis, Fed. Proc. **9**:363, 1950.
69. Kuhns, W. J., and Crittenden, J.: Zone Electrophoresis in Studies of Serum Proteins, Protein-bound Polysaccharides and Serum Lipids in Rheumatoid Disease, J. Lab. & Clin. Med. **46**:398, 1955.
70. Lansbury, J., Allen, G. E., and Rogers, F. B.: Failure of Skin Testing to Detect Antigen-antibody Properties in the Tissues of Rheumatoid Arthritis, Am. J. Med. Sc. **229**:191, 1955.
71. Lansbury, J., Crosby, W. R., and Bello, C. T.: Precipitin Reaction of Serum From Cases of Rheumatoid Arthritis With Homologous Connective Tissue Extracts, Am. J. Med. Sc. **220**:414, 1950.
72. Lefkovits, A. M., and Farrow, I. J.: The Liver in Rheumatoid Arthritis, Ann. Rheumat. Dis. **14**:162, 1955.
73. Lemon, H. M., Chasen, W. H., and Looney, J. M.: Abnormal Glycine Metabolism in Rheumatoid Arthritis, J. Clin. Invest. **31**:993, 1952.
74. Long, D. A., and Miles, A. A.: Opposite Action of Thyroid and Adrenal Hormones in Allergic Hypersensitivity, Lancet **1**:492, 1950.
75. Long, D. A., Miles, A. A., and Perry, W. L.: Action of Ascorbic Acid on Tuberculin Sensitivity in Guinea Pigs and Its Modification by Dietary and Hormonal Factors, Lancet **1**:1085, 1951.
76. Long, D. A., Miles, A. A., and Perry, W. L.: Action of Dehydroascorbic Acid and Alloxan on Tuberculin-sensitivity in Guinea Pigs, Lancet **2**:902, 1951.
77. Lospalluto, J., and Ziff, M.: Purification of the Accessory Agglutinating Factor of the Serum in Rheumatoid Arthritis, Proc. Ann. Meeting, ARA, Chicago, June, 1956, Bull. Rheumat. Dis. **7**:114, 1956.
78. Lovell, R. R. H., Goodman, H. C., Hudson, B., Armitage, P., and Pickering, G. W.: Effects of Cortisone and Adrenocorticotrophic Hormone on Experimental Inflammations in Human Skin, Clin. Sc. **12**:41, 1953.
79. Lovgren, O.: Rheumatoid Arthritis and the Liver, Ann. med. int. Fenniae **42**:42, 1953.
80. MacKenzie, K. R., Johnson, L. G., and Stacey, C. H.: Serum Mucoproteins and Electrophoretic Patterns in Rheumatic Diseases, Ann. Rheumat. Dis. **15**:269, 1956.
81. Maurer, P. H., and Lebovitz, H.: Antigenicity of Modified Fluid Gelatin, J. Immunol. **76**:335, 1956.
82. McEwen, C., Wilson, H., Ziff, M.: Studies on the Metabolism of Adrenal Cortical Steroids in the Synovial Cavity in Rheumatoid Arthritis, Tr. A. Am. Physicians **67**:97, 1954.
83. McKee, K. T., and Swineford, O.: Homologous Tissue Sensitization: Failure to Produce Joint and Kidney Lesions or Precipitins With Homologous Tissue Plus Streptococci, Ann. Rheumat. Dis. **10**:116, 1951.
84. Meyer, K.: Biological Significance of Hyaluronic Acid and Hyaluronidase, Physiol. Rev. **27**:335, 1947.
85. More, R. A.: Relation of the Lesions of Hypersensitivity to the Collagen Diseases, Am. J. Path. **26**:702, 1950.
86. Movitt, E. R., and Davis, A. E.: Liver Biopsy in Rheumatoid Arthritis, Am. J. M. Sc. **226**:516, 1953.
87. Nelson, D. H., Samuels, L. T., Willardson, D. C., and Tyler, F. H.: The Levels of 17-Hydroxycorticosteroids in the Peripheral Blood of Human Subjects, J. Clin. Endocrinol. **11**:1021, 1951.
88. Norymberski, J. K., Stubbs, R. D., and West, H. F.: Assessment of Adrenocortical Activity by Assay of 17-Ketogenic Steroids in Urine, Lancet **1**:1276, 1953.
89. Pearse, A. G. E.: The Hypophysis in Rheumatoid Arthritis, Lancet **1**:954, 1950.
90. Pearson, C. M.: Experimental Production of Arthritis in Rats, Proc. Soc. Exper. Biol. & Med. **91**:95, 1956.
91. Pemberton, R., and Foster, G. L.: Studies on Arthritis in the Army Based on 400 Cases. III, Arch. Int. Med. **25**:243, 1920.

VOL.
5
1957

92. Perkoff, G. T., Sandberg, A. A., Nelson, D. H., and Tyler, F. H.: Clinical Usefulness of Determination of Circulating 17-Hydroxycorticosteroids Levels, A. M. A. Arch. Int. Med. **93**:1, 1954.
93. Peterson, R. E.: Pharmacology and Rate of Metabolism of Hydrocortisone, Cortisone, and Metacortandracin, and the Rate of Synthesis of Hydrocortisone in Man, Ann. Rheumat. Dis. **14**:422, 1955.
94. Peterson, R. E., Wyngaarden, J. B., Guerra, S. L., Brodie, B. B., and Bunim, J. J.: The Physiological Disposition and Metabolic Fate of Hydrocortisone in Man, J. Clin. Invest. **34**:1779, 1955.
95. Plotz, C. M.: In discussion on: "Haemagglutination Test for Rheumatoid Arthritis," Ann. Rheumat. Dis. **13**:321, 1953.
96. Plotz, C. M., and Singer, J.: Latex Fixation Test in Rheumatoid Arthritis. Proc. Ann. Meeting, ARA, Chicago, June, 1956, Bull. Rheumat. Dis. **7**:114, 1956.
97. Preston, W. S.: Arthritis in Rats Caused by Pleuropneumonia-like Micro-organisms and the Relationship of Similar Organisms to Human Rheumatism, J. Infect. Dis. **70**:180, 1942.
98. Rawls, W. B., Weiss, S., and Collins, V. L.: Liver Function in Rheumatoid (Chronic Infectious) Arthritis: Preliminary Report, Ann. Int. Med. **10**:1021, 1936.
99. Reinhardt, W. O., and Li, C. H.: Experimental Production of Arthritis in Rats by Hypophyseal Growth Hormone, Science **117**:295, 1953.
100. Rich, A. R.: Hypersensitivity in Disease, Harvey Lect. **42**:106, 1946.
101. Robinson, G. L.: A Study of Liver Function and Plasma Volume in Chronic Rheumatism by Means of Phenol-tetrabromphthalein Sodium Sulphonate, Ann. Rheumat. Dis. **3**:207, 1943.
102. Robinson, D. W., and Block, W. D.: Protein Metabolism in Rheumatoid Arthritis, J. Lab. & Clin. Med. **32**:1551, 1947.
103. Roy, L. M. H., Wigzell, F. W., Demers, R., Sinclair, R. J. G., Duthie, J. J. R., Atherden, S. M., and Marrian, G. F.: Liver Function in Relation to Possible Abnormalities of Steroid Metabolism in Rheumatoid Arthritis, Ann. Rheumat. Dis. **14**:183, 1955.
104. Sabin, A. B.: Experimental Proliferative Arthritis in Mice Produced by Filterable Pleuropneumonia-like Organisms, Science **90**:18, 1939.
105. Salt, H. B.: Serum Globulin Fractions in Chronic Rheumatic Diseases, Clin. Chem. **2**:35, 1956.
106. Shichikawa, K., Asano, N., Orihara, M., Mayeda, A., Tamatani, Y., and Yasuda, J.: Studies on the Waaler-Rose Haemagglutination Test. III. AAF and Anti-Complementary Activities, Acta. rheumat. scandinav. **2**:55, 1956.
107. Smyth, C. J., and Clark, G. M.: Relationship of the Polysaccharide Content of the Euglobulin Fraction in Rheumatoid Arthritis Serum to the Agglutination of Sensitized Sheep Erythrocytes, Ann. Rheumat. Dis. **15**:75, 1956.
108. Sokoloff, L., Sharp, J. T., and Kaufman, E. H.: Adrenal Cortex in Rheumatic Diseases With Special Reference to the Effects of Cortisone and ACTH, Ann. Rheumat. Dis. **10**:467, 1951.
109. Sommerville, I. F., Marrian, G. F., Duthie, J., Jr., and Sinclair, R. R. G.: Abnormality in Steroid Metabolism Associated With Rheumatoid Arthritis, Lancet **1**:116, 1950.
110. Starin, W. A.: The antigenic Properties of Gelatin, J. Infect. Dis. **23**:139, 1918.
111. Staub, P. L., Menthe, J. W., Nelson, S. S., and Cohn, H.: Excretion of 11-Oxycorticosteroids in Paraplegic and Rheumatoid Arthritis Patients, J. Clin. Invest. **29**:349, 1950.
112. Steinberg, C. L., and Suter, L. C.: Phosphatase Activity in Chronic Arthritis, Arch. Int. Med. **64**:483, 1939.
113. Svartz, N.: Serological Tests in Rheumatoid Arthritis, Lancet **2**:194, 1956.
114. Svartz, N., and Olhagen, B.: Electrophoretic Analysis of Proteins in Articular Rheumatism, Acta med. scandinav. **130**:456, 1948.
115. Svartz, N., and Schlossmann, K.: Cold Precipitable Agglutinating Factor in Serum From Patients With Rheumatoid Arthritis, Ann. Rheumat. Dis. **14**:191, 1955.
116. Thorn, G. W., and Bayles, T. B.: Pituitary-adrenal Function and Rheumatic Disease, Practitioner **163**:365, 1949.
117. Tyler, F. H., Schmidt, C. D., Eik-Nes, K., Brown, H., and Samuels, L. T.: The Role of the Liver and Adrenal in Producing Elevated Plasma 17-Hydroxycorticosteroid Levels in Surgery, J. Clin. Invest. **33**:1517, 1954.
118. Vaughan, J. H.: Behaviour of the Agglutination Activating Factor of Rheumatoid Arthritis With Immune Precipitates, Ann. Rheumat. Dis. **14**:431, 1955.
119. Vaughan, J. H.: Behaviour of the Rheumatoid Arthritis Agglutinating Factor With Immune Precipitates, J. Immunol. **77**:181, 1956.
120. Vaughan, J. H., Armato, A., Goldthwait, J. C., Brachman, P., Favour, C. B., and Bayles, T. B.: A Study of Gamma Globulin in Rheumatoid Arthritis, J. Clin. Invest. **34**:75, 1955.
121. Vaughan, J. H., Bayles, T. B., and Favour, C. B.: Serum Complement in Rheumatoid Arthritis, Am. J. M. Sc. **222**:186, 1951.
122. Waksman, B. H., and Mason, H. L.: Antigenicity of Collagen, J. Immunol. **63**:427, 1949.

VOL 5 195

123. Wallerstein, R., Vallee, B., and Turner, L.: Possible Relationship of the Pleuropneumonia-like Organisms to Reiter's Disease, Rheumatoid Arthritis, and Ulcerative Colitis, J. Infect. Dis. **79**:134, 1946.
124. Wallis, A. D.: Serum Proteins in Rheumatoid Arthritis, Ann. Int. Med. **32**:63, 1950.
125. Ward, L. E., Chung, W. V., Hench, P. S., Mason, H. L., Slocumb, C. H., Polley, H. F., and Mayne, J. G.: Hydrocortisone in Plasma of Normal Individuals and Patients With Certain Rheumatic Diseases, Bull. Rheumat. Dis. **7**:115, 1956.
126. Ward, L. E., Polley, H. F., Slocumb, C. H., Hench, P. S., Mason, H. L., Mattox, V. R., and Power, M. H.: Effects of Aldosterone (Electrocortin) and of 9-a-fluoro-hydrocortisone Acetate on Rheumatoid Arthritis: Preliminary Report, Proc. Mayo Clin. **29**:649, 1954.
127. Warren, J. E.: Diurnal Plasma Corticoid Studies and Their Relation to Morning Stiffness in Rheumatoid Arthritis, Bull. Rheumat. Dis. **7**:115, 1956.
128. Watson, R. F., Rothbard, S., and Vanamee, P.: The Antigenicity of Rat Collagen, J. Exper. Med. **99**:535, 1954.
129. Wayne, E. J., Goodwin, J. F., and Stoner, H. B.: Effect of Adenosine Triphosphate on the Electrocardiogram of Men and Animals, Brit. Heart J. **11**:55, 1949.
130. Wedgewood, R. J. P., and Janeway, C. A.: Serum Complement in Children with "Collagen Diseases," Pediatrics **11**:569, 1953.
131. Wells, B. B., Lowry, R. D., and Ross, S. W.: Laboratory Procedures for Rheumatoid Arthritis; Critical Survey of Tests Used in Diagnosis and Treatment, Am. J. Clin. Path. **21**:423, 1951.
132. Wichelhausen, R. H., Brown, T. M., Robinson, L. B., and Merchant, W. R.: Pleuropneumonia-like Organisms and Their Possible Significance in Collagenous Diseases, Ann. Rheumat. Dis. **10**:463, 1951.
133. Wilson, H., Glyn, J., Scull, E., McEwen, C., and Ziff, M.: Rate of Disappearance and Metabolism of Hydrocortisone and Cortisone in the Synovial Cavity in Rheumatoid Arthritis, Proc. Soc. Exper. Biol. **83**:648, 1953.
134. Winblad, S.: Studies on Agglutination of Sensitized Sheep Cells in Rheumatic Diseases. II. On the Nature of the Agglutinating Serum Factor, Acta med. scandinav. **142**:458, 1952.
135. Ziff, M., Brown, P., LosPalluto, J., Badin, J., and McEwen, C.: Agglutination and Inhibition by Serum Globulin in the Sensitized Sheep Cell Agglutination Reaction in Rheumatoid Arthritis, Am. J. Med. **20**:500, 1956.
136. Ziff, M., Kibrick, A., Dresner, E., and Gribbetz, H. J.: Excretion of Hydroxyproline in Patients With Rheumatic and Non-rheumatic Diseases, J. Clin. Invest. **35**:579, 1956.

OL.
5
957

PROPOSED DIAGNOSTIC CRITERIA FOR RHEUMATOID ARTHRITIS

Report of a Study Conducted by a Committee of the American Rheumatism Association

M. W. Ropes, Chairman, and G. A. Bennett, S. Cobb, R. Jacox, and R. A. Jessar

(Received for publication Feb. 5, 1957.)

VOL 5 195

DIAGNOSIS of rheumatoid arthritis is easy to make in typical, severe cases, but in many of the less typical cases it is often difficult since there is no available proof of the diagnosis. As a result there is little uniformity in the cases included in any series labeled rheumatoid arthritis.[1] Consequently, comparison of studies from one physician or clinic with those from another is difficult—whether the studies relate to prevalence, incidence, manifestations, course, treatment or other features of the disease.

In order to obtain more uniformity in cases listed as rheumatoid arthritis, a committee of the American Rheumatism Association on diagnostic criteria was formed, with full realization that it would be very difficult to determine the limits of the diagnosis "rheumatoid arthritis." In view of this difficulty, it seemed wise to classify rheumatoid arthritis in three categories—definite, probable and possible. In the definite group there should be almost no question that every patient has rheumatoid arthritis and in the probable group the likelihood should be great that every patient has rheumatoid arthritis. These two groups should be used for any study or report of the characteristics, course and treatment of rheumatoid arthritis. The criteria for the third, the "possible" group, are much less rigid and, of necessity, some patients who do not have rheumatoid arthritis will be included in this category. Only by having liberal criteria in this group, however, will it be possible to pick up early and atypical cases which can be followed profitably to learn more of the course and nature of the disease. The inclusion of patients who do not have rheumatoid arthritis will not be serious. Errors in diagnosis will become apparent as the patients in this category are followed, and at no time can this group be used for definite conclusions concerning the characteristics or treatment of rheumatoid arthritis. The criteria are designed not so much to aid a physician in making a diagnosis in an individual case, but rather to establish the findings necessary to allow inclusion of a patient in one or another of the categories.

In selecting the individual criteria for use, it was at once apparent that many of the signs and symptoms of the disease are entirely non-specific and of

Reprinted from the *Bulletin on Rheumatic Diseases*, December, 1956, by permission of the Arthritis and Rheumatism Foundation; the authors and the Editor.

no value in differential diagnosis and therefore not useful in allocation of patients to the categories. The majority of these non-specific findings are indications of the systemic involvement in the disease—as, for instance, fatigue, anorexia, fever, lymphadenopathy, anemia, leukocytosis or leukopenia. Others, indicative of musculoskeletal inflammation and its sequelae—tenosynovitis, muscle atrophy, skin atrophy—are also relatively non-specific and are not included. The final selection of appropriate criteria was made in the following manner. On the basis of the clinical experience of the members of the committee, a list was formed of all of the manifestations of rheumatoid arthritis which might have sufficient diagnostic value to be worthy of consideration. Data from the Pittsburgh Arthritis Study[1,2] were then examined to give indication of the diagnostic value of the various manifestations. Finally, data were collected from a number of physicians particularly interested in rheumatic diseases in various sections of the United States and Canada.* Each physician was asked to select from his clinic or practice the most recent five cases of classical rheumatoid arthritis, five of probable rheumatoid arthritis, and five with no evidence of rheumatoid arthritis. On each case a detailed form was filled out from the record. In all, 332 suitable case reports were received from nineteen different cities. These were analyzed to give further information about the diagnostic value of the signs, symptoms, and laboratory tests, individually and in various combinations.

The features that were shown, on the basis of these analyses, to be of too little value were eliminated. The following manifestations fall into this category: weight loss, vasomotor symptoms, paresthesias, splenomegaly, pericarditis, myocarditis, pleurisy, reversal of the albumin/globulin ratio in the plasma and thickening of the palmar fascia. From the remaining criteria the manifestations shown to have the highest specificity were chosen as the criteria for the diagnosis of definite and probable rheumatoid arthritis. For the category of possible rheumatoid arthritis, characteristics with the highest sensitivity, with or without high specificity, were selected. From a study of the relationship between the number of major criteria and the diagnoses reported by the American Rheumatism Association physicians, it was concluded that five of the listed eleven criteria should be required for allocation of a patient to the category of "definite rheumatoid arthritis" and that three be required for "probable rheumatoid arthritis."

An attempt was made, as discussed above, to make the criteria for definite and probable rheumatoid arthritis rigid enough to be as sure as possible that all cases included have rheumatoid arthritis. This was essential since patients included in these categories will be used for study of the disease and often serve as a basis for statistical conclusions as to prevalence, incidence, characteristics, course and treatment. It is important, however, that the criteria not be so strict that only cases of great severity or long duration can be included. Therefore the duration required for allocation to these categories was made as short as possible (6 weeks and 4 weeks), but long enough to tend to exclude infectious

*We wish to acknowledge the valuable contribution made by these physicians.

and traumatic arthritis and, in general, rheumatic fever. Also, as small a number of joints was required as possible—only one, if other adequate clinical or laboratory evidence, such as characteristic histologic changes in synovial tissues or nodules, is present.

The criteria as listed below need not be discussed individually. Morning stiffness may be either subjective or objective and vary from a feeling of stiffness to actual limitation of motion. By definition it disappears or decreases during the day. It may persist for only a few minutes or last many hours. The evidence of joint involvement must be objective and must be observed by a physician—though all observations need not necessarily be made by the same physician. Emphasis should be laid on the fact that the swelling cannot be bony enlargement alone but must be soft tissue thickening or actual effusion. When two joints are not involved simultaneously, they may satisfy the criterion of involvement of more than one joint if there is no interval free of joint symptoms of more than three months. If the interval were longer the possibility of two separate types of joint disease being present would be greater. Symmetry of joint involvement is acceptable as a criterion in any joints except the terminal phalangeal joints. The latter are excluded to lessen the likelihood of false inclusion of patients with the characteristic symmetrical terminal phalangeal joint involvement of degenerative joint disease. The presence of x-ray abnormalities characteristic of degenerative joint disease will not satisfy the criterion but the presence of such x-ray changes will not exclude a patient from any of the categories of rheumatoid arthritis. It is important not to exclude a patient who has rheumatoid arthritis because he has also degenerative joint disease—an error that is commonly made. Uncomplicated degenerative joint disease is excluded, we hope, by the rigid criteria (soft tissue swelling, symmetry—not limited to the terminal phalangeal joints, nodules and laboratory findings). Of the abnormalities in synovial fluid the nature of the mucin precipitate is the most characteristic and most easily determined. Other abnormalities, especially increased activity of aminotripeptidase or betaglucuronidase, will add weight to the diagnosis, but are not included as specific criteria.

In all respects the criteria for possible rheumatoid arthritis are less strict. The required duration of symptoms is reduced to 3 weeks. A history, rather than observation, of joint swelling is adequate. Non-specific laboratory abnormality such as elevated sedimentation rate, is acceptable. Iritis was included as a criterion because of the relative frequency with which rheumatoid arthritis is the cause. Pericarditis, myocarditis and pleurisy were omitted because they are more frequently due to other diseases than to rheumatoid arthritis, and would lead to false inclusion of many patients.

Thus, the criteria were established. Since, however, similar combinations of findings occur in many other rheumatic diseases, the latter can be excluded only by specifically listing them as exclusions. In some cases it is possible that patients with one of these other diseases (for instance, one of the generalized connective tissue diseases other than rheumatoid arthritis or other rheumatic disease such as gout) may be thought to have rheumatoid arthritis also. For example, a patient with a history suggesting rheumatic fever and with physical findings of mitral and aortic valvular disease may also have a recent history and

findings of definite rheumatoid arthritis. In such a situation, however, it seems wisest not to include the patient in a study of rheumatoid arthritis but to classify him separately and compare as desired. On the other hand, patients with rheumatoid spondylitis (x-ray changes in sacro-iliac joints or persistent limitation of motion of any region of the spine not due to another form of spinal disease) or with psoriasis, or with ulcerative colitis, or with onset under the age of 12, are to be included in the rheumatoid groups, if they satisfy the criteria, but should be listed separately and the results of studies pertaining to them be given separately.

The exclusions may rule out a few cases of rheumatoid arthritis but this, we think, will rarely occur and will not be as serious as including more patients who do not have rheumatoid arthritis. The exclusions need not be discussed in detail—in general the clinical findings or picture are so well known there will be no questions. Some have questioned the L.E. cell exclusion. There is difference of opinion as to the specificity of this test. Some physicians think that one L.E. cell proves the diagnosis of disseminated lupus erythematosus, and rules out rheumatoid arthritis. Many others think that L.E. cells may be found in three to five per cent of rheumatoid patients.[3] However, since all apparently agree that a high concentration of cells proves disseminated lupus, 4 cells in 2 smears with the heparin method incubated not over 2 hours are adequate to exclude a patient from the rheumatoid groups.

The present criteria are as follows.

VOL.
5
1957

DEFINITE RHEUMATOID ARTHRITIS

This diagnosis requires 5 of the following criteria and total duration of joint symptoms must be at least 6 weeks. (Any one of the features listed under "Exclusions" will exclude a patient from this category.)

1. Morning stiffness.
2. Pain on motion or tenderness in at least one joint (observed by a physician).
3. Swelling (soft tissue thickening or fluid—not bony overgrowth alone) in at least one joint (observed by a physician).
4. Swelling (observed by a physician) of at least one other joint (any interval free of joint symptoms between the two joint involvements may not be more than 3 months).
5. Symmetrical joint swelling (observed by a physician) with simultaneous involvement of the same joint on both sides of the body (bilateral involvement of mid-phalangeal, metacarpophalangeal or metatarso-phalangeal joints is acceptable without absolute symmetry). Terminal phalangeal joint involvement will not satisfy this criterion.
6. Subcutaneous nodules (observed by a physician) over bony prominences, on extensor surfaces or in juxta-articular regions.
7. X-ray changes typical of rheumatoid arthritis (which must include at least bony decalcification localized to or greatest around the involved joints and not just degenerative changes)—degenerative changes do not exclude patients from the group of rheumatoid arthritis.

8. Positive sheep cell agglutination (Rose and Ragan,[4] or Heller[5] test) or positive streptococcal agglutination test.

9. Poor mucin precipitate from synovial fluid (with shreds and cloudy solution).

10. Characteristic histologic changes in synovial membrane with 3 or more of the following: marked villous hypertrophy; proliferation of superficial synovial cells often with palisading; marked infiltration of chronic inflammatory cells (lymphocytes or plasma cells predominating) with tendency to form "lymphoid nodules"; deposition of compact fibrin, either on surface or interstitially; foci of cell necrosis.

11. Characteristic histologic changes in nodules showing granulomatous foci with central zones of cell necrosis, surrounded by proliferated fixed cells, and peripheral fibrosis and chronic inflammatory cell infiltration, predominantly perivascular.

PROBABLE RHEUMATOID ARTHRITIS

This diagnosis requires 3 of the above criteria and total duration of joint symptoms must be at least 4 weeks. (Any one of the features listed under "Exclusions" will exclude a patient from this category.)

POSSIBLE RHEUMATOID ARTHRITIS

This diagnosis requires 2 of the following criteria and total duration of joint symptoms must be at least 3 weeks. (Any one of the features listed under "Exclusions" will exclude a patient from this category.)

1. Morning stiffness.
2. Tenderness or pain on motion (observed by a physician) with history of recurrence or persistence for 3 weeks.
3. History or observation of joint swelling.
4. Subcutaneous nodules (observed by a physician).
5. Elevated sedimentation rate or C-reactive protein.
6. Iritis.

EXCLUSIONS

1. The typical rash of *disseminated lupus erythematosus* (with butterfly distribution, follicle plugging and areas of atrophy).
2. High concentration of *lupus erythematosus cells* (4 or more in 2 smears prepared from heparinized blood incubated not over 2 hours).
3. Histologic evidence of *periarteritis nodosa* with segmental necrosis of arteries associated with nodular leukocytic infiltration extending perivascularly and tending to include many eosinophils.
4. Weakness of neck, trunk and pharyngeal muscles or persistent muscle swelling of *dermatomyositis.*
5. Definite *scleroderma* (not limited to the fingers).
6. A clinical picture characteristic of *rheumatic fever* with migratory joint involvement and evidence of endocarditis, especially if accompanied by subcutaneous nodules or erythema marginatum or chorea. (An elevated antistreptolysin titer will not rule out the diagnosis of rheumatoid arthritis.)

7. A clinical picture characteristic of *gouty arthritis* with acute attacks of swelling, redness and pain in one or more joints, especially if relieved by colchicine.

8. Tophi.

9. A clinical picture characteristic of acute *infectious arthritis* of bacterial or viral origin with: an acute focus of infection or in close association with a disease of known infectious origin; chills; fever; and an acute joint involvement, usually migratory initially, (especially if there are organisms in the joint fluid or response to antibiotic therapy).

10. *Tubercle bacilli* in joints or histological evidence of joint tuberculosis.

11. A clinical picture characteristic of *Reiter's syndrome* with urethritis and conjunctivitis associated with acute joint involvement, usually migratory initially.

12. A clinical picture characteristic of the *shoulder-hand syndrome* with unilateral involvement of shoulder and hand, with diffuse swelling of the hand followed by atrophy and contractures.

13. A clinical picture characteristic of *hypertrophic pulmonary osteoarthropathy* with clubbing of fingers and/or hypertrophic periostitis along the shafts of the long bones, especially if an intrapulmonary lesion is present.

14. A clinical picture characteristic of *neuroarthropathy* with condensation and destruction of bones of involved joints and with associated neurological findings.

15. *Homogentisic acid* in the urine detectable grossly with alkalinization.

16. Histological evidence of *sarcoid* or positive Kveim test.

17. *Multiple myeloma* as evidenced by marked increase in plasma cells in the bone marrow, or Bence-Jones protein in the urine.

18. Characteristic skin lesions of *erythema nodosum*.

19. *Leukemia* or *lymphoma* with characteristic cells in peripheral blood, bone marrow or tissues.

These tentative criteria are presented now for general use and evaluation. The necessity for changes to modify the criteria or clarify the statements will become apparent as they are used. The criteria should be officially reviewed within two years and revised as necessary. However, it is our hope that, even in the present form, they will aid in making it apparent to all, just what cases are included in any group of rheumatoid patients that is discussed or reported.

VOL.
5
1957

REFERENCES

1. Cobb, S., Merchant, W. R., and Warren, J. E.: J. CHRON. DIS. **2**:50, 1955.
2. Cobb, S., Thompson, D. J., Rosenbaum, J., Warren, J. E., and Merchant, W. R.: J. CHRON. DIS. **3**:134, 1956.
3. Discussion of paper by McCoy, F. W., Patterson, M., and Freyberg, R. H.: Ann. Rheumat. Dis. **14**:415, 1956.
4. Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O.: Proc. Soc. Exper. Biol. & Med. **68**:1, 1948.
5. Heller, G., Jacobson, A. S., and Kolodny, M. H.: Proc. Soc. Exper. Biol. & Med. **72**:316. 1949.

AN ESTIMATE OF THE PREVALENCE OF RHEUMATOID ARTHRITIS

SIDNEY COBB, M.D., M.P.H., JOSEPH E. WARREN, M.D., WILLIAM R. MERCHANT, M.D., AND DONOVAN J. THOMPSON, PH.D.

PITTSBURGH, PA.

From the Graduate School of Public Health and the School of Medicine, University of Pittsburgh

(Received for publication Feb. 5, 1957.)

VOL
5
195

IN 1933, Dublin[7] stated "Statistics of sickness from rheumatism suffer from the defects of most morbidity statistics of diseases which are not required by law to be reported to public health officers; they are collected in special studies at more or less frequent intervals over short periods of time, at different seasons, over small areas, or for relatively small populations, most of them selected and unrepresentative groups. The methods of collection of data are not uniform and the results are variously interpreted and often contradictory." Since 1933, the prevalence of rheumatoid arthritis, which is the principal crippler among the rheumatic diseases, has been reported from a number of surveys in several countries (Table I). To date no adequate data have been presented from the United States.

The several reports listed in Table I cannot be compared for the various reasons mentioned by Dublin. Perhaps the most important of these reasons is the almost uniform lack of any specified and reasonably reproducible criteria for the diagnosis of rheumatoid arthritis. The report by Miall[14] is the first to give proper attention to this most important aspect of any survey.

The American Rheumatism Association has recently accepted a set of criteria for the diagnosis of rheumatoid arthritis.[15] These criteria recognize a separation into definite, probable, and possible rheumatoid arthritis. They form the basis for classification in this report.

It should be noted that no statistics from medical care organizations have been included in Table I. The reason for this is that another variable is introduced by the inclusion of such figures because a rather special type of prevalence, sometimes referred to as a time prevalence, is obtained from such data. The best way to explain the difference between the usual "point" prevalence and the "time" prevalence is to give an illustration. From Sweden, we have the report of Edström[8] that at the time of his survey (summer, 1943), 2 per cent of the population had rheumatoid arthritis that was recognizable by the staff of especially trained medical students that he sent into the areas selected for study.

Publication No. 9 of the Pittsburgh Arthritis Study. Supported in part by Grant No. A-308 and in part by the Western Pennsylvania Chapter of the Arthritis and Rheumatism Foundation.

This is a point prevalence estimate. Quite different from this is the report by Bohman[2] that during the year 1943, 2.5 per cent of the population of Sweden sought medical treatment for rheumatoid arthritis. This is an annual prevalence. In addition, the count is not of the number of afflicted persons but rather of the number of afflicted persons who requested treatment, which is quite another matter.

This report is concerned primarily with the point prevalence of rheumatoid arthritis as defined by the American Rheumatism Association.[15]

METHODS

The details of the field procedures in the Pittsburgh Arthritis Study have been set forth in earlier papers in this series.[3-5] For present purposes it is sufficient to know that a stratified random sample of 798 individuals over 14 years of age from the Arsenal Health District of Pittsburgh was selected, using different sampling rates in the several strata. Eighty-nine per cent of these individuals were interviewed and 60 per cent of them were examined. A comparison of the respondents for the examination with those who refused[5] has demonstrated a bias in favor of response by those giving an interview report of arthritis or one of its manifestations. Furthermore, study of the 478 individuals who were interviewed and examined has revealed that a set of three questions relating to arthritis and rheumatism, morning stiffness, and joint swelling forms a good index of rheumatoid arthritis[17] (sensitivity 66 per cent and specificity 95 per cent). In order to correct for the observed bias the material has been further poststratified on this index.

The interviews and the examinations which included x-rays but no serologic tests were conducted during the period from May, 1953, through September, 1954. The results of the examinations were recorded in great detail on a printed form so that in the summer of 1956, when the criteria for the diagnosis of rheumatoid arthritis were fixed by the American Rheumatism Association, we were able to review the material in the light of these criteria and classify it accordingly.

On completion of the first set of examinations, it was noted that there were 223 persons who had reported morning stiffness or had had other indication of possible rheumatoid arthritis. Further information was obtained on 88 per cent of these people approximately one year after their first examination. Sixty-eight per cent were re-examined in detail at the Health Center. Further x-rays were taken as indicated, blood was drawn for sedimentation rates, and a sample of serum was frozen for serologic studies. Sensitized sheep cell agglutination tests were performed in the laboratory of Dr. Charles Ragan by the method originally described by Rose and associates.[16] As a result of this second examination, additional cases were classified as rheumatoid arthritis. These are reported only in the discussion of annual prevalence.

RESULTS

In Table II are presented the point prevalence estimates for rheumatoid arthritis. The prevalence estimate of 0.7 per cent for definite rheumatoid arthritis is based on only 13 cases, and, therefore, cannot be considered very stable.

TABLE I. SUMMARY OF RECENT SURVEY ESTIMATES OF THE PREVALENCE OF RHEUMATOID ARTHRITIS

COUNTRY	AUTHORS	PREVALENCE			AGE GROUP	COMMENT
		M	F	TOTAL		
Great Britain	Kellgren et al.[11]	1.4	3.3	(2.4)	15+	Clinical diagnosis based on a brief examination in the home
Great Britain	Kellgren and Lawrence[12]	2.5	11.0	(7.8)	55-64	Clinical diagnosis based on careful examination plus laboratory and x-ray findings
Great Britain	Miall[14]	0.7	—	—	15+	Polyarthritis + positive DAT or x-ray
Sweden	Edström[8]	(1.3)	(2.7)	2.0	All	"Chronic arthritis" recognized by especially trained medical students in the home
Netherlands	de Blécourt[1]	—	—	1.0	14+	Clinical diagnosis based on a brief examination
Finland	Holsti and Rantasalo[10]	(0.3)	(0.9)	(0.6)	All	"Chronic arthritis" known to Public Health Nurses in their own districts
Slovakia	Sitaj et al.[13]	—	—	0.5	15-45	Clinical diagnosis based on careful examination and some laboratory and x-ray findings
Greenland	Ehrstrom[9]	—	—	(0.3)	5+	Clinical diagnosis
United States	This report	0.6	4.7	2.7	15+	ARA definitions, probable and definite by examination and x-ray findings

( ) = Our computations from data presented by the authors.

VOL 5 1957

However, the estimate of 2.7 per cent of the population with probable or definite rheumatoid arthritis is rather more reliable.

TABLE II. THE PREVALENCE OF RHEUMATOID ARTHRITIS (ARA DEFINITIONS) IN THE ARSENAL HEALTH DISTRICT OF PITTSBURGH, 1953-1954. RATES PER 100 PERSONS 15 YEARS OF AGE AND OVER

	RATE PER 100 PERSONS	NUMBER OF CASES
Definite	0.7	13
Probable + definite	2.7	30
Possible + probable + definite	13.9	107

Using consideration 13.2 in Cochran's[6] test, we get an estimate that there are only 25 chances in 1,000 that the true value is below 1.2 per cent. Cochran's consideration 13.3 does not seem to apply logically in considering the upper limit for we have been able to demonstrate[5] that there is a tendency for the rheumatoids to be among the respondents rather than among the nonrespondents. Therefore, the assumption that all of the nonrespondents might have rheumatoid arthritis seems foolish. We prefer to believe that there is only about 2½ per cent chance that the true value exceeds 2.7 + 2 S.E., i.e., 4.1 per cent. We are aware of the imperfections of confidence interval estimation in this kind of situation, but present the results as a guide to those who might be tempted to make comparisons with data from other areas.

The value of about 14 per cent for total rheumatoid arthritis may be surprising to some. However, when it is realized from studying the criteria that this is essentially a statement of the proportion of persons having morning stiffness and joint tenderness or pain on motion, it is perhaps less disturbing.

The prevalence rates by sex are shown in Table III. It is admittedly foolish to subdivide the definite cases by sex for the estimates are certainly quite unstable. This has been done merely to emphasize the difference between this ratio of 2.5 women to 1 man, which is in line with usual clinical experience, and the extraordinarily high value that is obtained for probable rheumatoid arthritis.

TABLE III. PREVALENCE BY SEX, AND SEX RATIOS, FOR RHEUMATOID ARTHRITIS (ARA DEFINITIONS) IN THE ARSENAL HEALTH DISTRICT OF PITTSBURGH, 1953-1954. RATES PER 100 PERSONS 15 YEARS OF AGE AND OLDER

	MALES	FEMALES	RATIO F/M
Definite	0.4	1.0	2.5
Probable	0.2	3.7	18.5
Possible	10.6	11.7	1.1

Detailed examination of the data suggests two reasons for this high sex ratio. The first is that a great deal of mild rheumatoid arthritis occurs among older women. This is in line with the experience of Kellgren and Lawrence[12] whose data on the age group 55 to 64 suggest a ratio of 11.5 women to 1 man for mild rheumatoid arthritis. The second factor likely to be operating here is the possibility that 0.2 per cent is an underestimate of the prevalence of probable rheu-

matoid arthritis in men, due simply to sampling variation. We are then inclined to believe that the true sex ratio for probable rheumatoid arthritis is high but that our estimate of 18.5 is too high.

The effect of age on the prevalence of rheumatoid arthritis is shown in Fig. 1. The most striking phenomenon is the rapid increase in total disease around the age of 25 years with relatively minor increases after that. The second point of interest about this diagram is that at least part of the increase with advancing age of probable plus definite disease seems to be at the expense of possible disease. The implication of this finding will be discussed below. The data are too meager to subdivide further by sex, but one gains the impression that the general shape of the age specific curves for the two sexes is the same, though the biggest increase for women comes in the forties and fifties and the biggest increase for men comes after the age of 65.

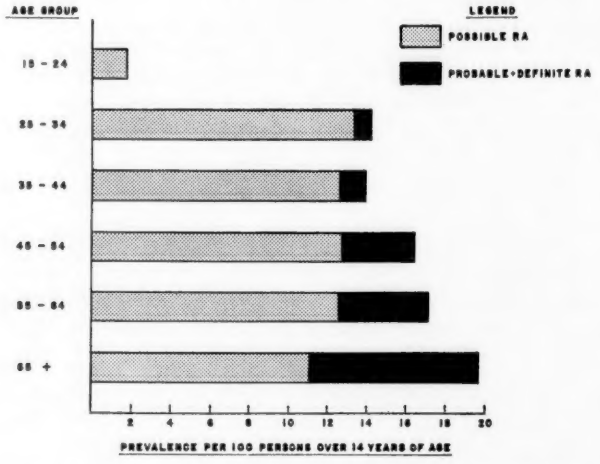

Fig. 1.—The prevalence of rheumatoid arthritis in Pittsburgh by age.

Routine analysis of morbidity data is often performed according to age, sex, and race. In the sample studied there are too few nonwhite persons to permit any analyses by race. However, we have analyzed this material on another basic human variable, namely marital status. The results are presented in Table IV. The differences between the rates for the single, the married, and those whose marriage has been terminated by separation, divorce, or death suggest that this is an area worthy of further study. Clearly these numbers are small, but they are supported by interview information which is not appropriately reported at this time. Furthermore, Lewis-Faning[13] has observed a somewhat similar phenomenon in England. It is interesting to note that both our material and that of Lewis-Faning suggest that this is more important for men than for women.

Up to now we have spoken only of point prevalence. As noted above, those with morning stiffness or otherwise suspect of rheumatoid arthritis were examined a second time for further evaluation. In so far as possible the second

examinations were performed about twelve months after the first. As a result it can be said that on performance of two examinations in a period of twelve months the rate for probable and definite rheumatoid arthritis is nearly doubled, going up to 5.1 per cent. This is not due to the use of the serologic test on the second examination for there was only one positive test found.

TABLE IV. THE PREVALENCE OF PROBABLE PLUS DEFINITE RHEUMATOID ARTHRITIS (ARA DEFINITIONS) IN THE ARSENAL HEALTH DISTRICT OF PITTSBURGH, 1953-1954 BY MARITAL STATUS. RATES PER 100 PERSONS 15 YEARS OF AGE AND OLDER, ADJUSTED FOR AGE AND SEX

	PER CENT WITH R. A.	NUMBER OF CASES
Single	0.9	2
Married	2.2	17
Marriage terminated	3.6	11

VOL.
5
957

We are not willing to hazard a guess as to the value of the true annual prevalence of the disease which should be based on three, four, or even six examinations in a year. We can say, however, that we are confident that in the Arsenal Health District of Pittsburgh at least 5 per cent of persons over 14 years of age have, in any given year, an attack of rheumatism that would meet the American Rheumatism Association criteria for probable or definite rheumatoid arthritis.

DISCUSSION

From the age and sex specific data come some suggestions about the nature of rheumatoid arthritis. First, the shape of the curve for prevalence by age suggest that something fundamental takes place in the early twenties. This might be either physiologic or environmental. This is, of course, the beginning of the child-bearing period for most women and we know that rheumatoid arthritis may have its onset during the post partum period. No such obvious physiologic changes are taking place in the male during this period, and yet the shape of the age specific curve is, as nearly as we can determine from our limited data, about the same for men and women. One might then ask if perhaps the important social changes of emancipation from parents and the assumption of family, community, and job responsibilities which usually take place during this period may have something to do with this striking phenomenon. Support for such a notion is found in the data on marital status wherein it is suggested that those who do not assume family responsibilities have less rheumatoid arthritis than those who marry.

There is one further point that should be discussed, namely, the observation that possible rheumatoid arthritis reaches its peak prevalence about the age of 30 and seems to decrease after that. Though the prevalence estimates for the individual age groups are not based on as many cases as might be desirable, the trend would suggest that the definition of possible rheumatoid arthritis is valid for it is possible to interpret the data as suggesting that the more severe forms

of the disease are, at least in part, drawn from the population of persons who have possible disease at the age of 30. This needs to be further investigated by long-term follow-up studies, for the fact that age and sex have little influence on the prevalence of possible rheumatoid arthritis after the age of 25 years, while they have considerable effect on probable and definite disease, raises the converse suggestion that these might be two separate diseases.

The findings reported here raise more questions than they answer. It is hoped that this report will stimulate further research on the prevalence and incidence of rheumatoid arthritis as they relate to such simple variables as age, sex, and marital status, and also more complex variables including psychologic, social, and cultural factors.

SUMMARY AND CONCLUSIONS

1. It is estimated that the prevalence of probable plus definite rheumatoid arthritis (ARA definitions) in the Arsenal Health District of Pittsburgh is approximately 2.7 per cent of the total population over 14 years of age. The specific rates increase with age and are higher for women than men. A further 11 per cent of this same group meet the criteria for possible rheumatoid arthritis. The age specific rates for this category show an abrupt rise in the twenties to a maximum in the thirties which is followed by a gradual fall.

2. It is estimated that at least 5 per cent of the persons over 14 years of age in the Arsenal Health District of Pittsburgh have each year an attack of rheumatism that would meet the American Rheumatism Association criteria for probable rheumatoid arthritis.

3. At the present time it is not appropriate to make geographic comparisons based on the studies reported from various countries nor is it justified to assume that the rates observed for the Arsenal Health District of Pittsburgh are applicable to other parts of the United States.

4. The evidence with regard to the effect of marital state on the prevalence of this disease suggests further investigation of cultural, social, and psychologic factors that might be related to the disease.

REFERENCES

1. Blécourt, de J. J.: Screening of the Population for Rheumatic Diseases, Ann. Rheumat. Dis. **13**:338, 1954.
2. Bohman, F.: The Social Importance of Rheumatic Diseases in Sweden, Acta med. scandinav. **132**:150, 1948.
3. Cobb, S., Thompson, D. J., Rosenbaum, J., Warren, J. E., and Merchant, W. R.: On the Measurement of Prevalence of Arthritis and Rheumatism from Interview Data, J. CHRON. DIS. **3**:134, 1956.
4. Cobb, S., and Rosenbaum, J.: A Comparison of Specific Symptom Data Obtained by Non-medical Interviewers and by Physicians, J. CHRON. DIS. **4**:245, 1956.
5. Cobb, S., King, S., and Chen, E.: Differences Between Respondents and Nonrespondents in a Morbidity Survey Involving Clinical Examinations, J. CHRON. DIS. (In press.)
6. Cochran, W. G.: Sampling Techniques, New York, 1953, John Wiley & Sons, Inc.
7. Dublin, L. I., in Wyatt, B. L.: Chronic Arthritis and Fibrositis, Diagnosis and Treatment, Baltimore, 1933, William Wood & Company.
8. Edström, G.: The Frequency of Rheumatic Diseases in Sweden, Upsala Lakarenforen. Forhandl. **49**:303, 1944. Translation by Stig Holmquist available in library of Graduate School of Public Health, University of Pittsburgh.
9. Ehrström, M. C.: Medical Studies in North Greenland, 1948-1949. V. Rheumatic Diseases. Comparative Investigation of the Incidence, Acta med. scandinav. **140**:412, 1951.

10. Holsti, O., and Rantasola, V.: On the Occurrence of Arthritis in Finland, Acta med. scandinav. **88**:180, 1936.
11. Kellgren, J. H., Lawrence, J. S., and Aitken-Swan, J.: Rheumatic Complaints in an Urban Population, Ann. Rheumat. Dis. **12**:5, 1953.
12. Kellgren, J. H., and Lawrence, J. S.: Rheumatoid Arthritis in a Population Sample, Ann. Rheumat. Dis. **15**:1, 1956.
13. Lewis-Faning, E.: Report on an Enquiry Into the Aetiological Factors Associated With Rheumatoid Arthritis, Ann. Rheumat. Dis. (Suppl.) **9**:1, 1950.
14. Miall, W. E.: Rheumatoid Arthritis in Males; An Epidemiological Study of a Welsh Mining Community, Ann. Rheumat. Dis. **14**:150, 1955.
15. Proposed Diagnostic Criteria for Rheumatoid Arthritis, Report of a Study Conducted by a Committee of the American Rheumatism Association, J. CHRON. DIS. **5**:630 ,1957.
16. Rose, H. M., Ragan, C., Pearce, E., and Lipman M. O.: Differential Agglutination of Normal and Sensitized Sheep Erythrocytes by Sera of Patients With Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **68**:1, 1948.
17. Rubin, T., Rosenbaum, J., and Cobb, S.: The Use of Interview Data for the Detection of Associations in Field Studies, J. CHRON. DIS. **4**:253, 1956.
18. Sitaj, S., Straka, L., Niepel, G.: The Occurrence of Rheumatic Diseases on the Basis of an Examination of the Population as a Whole, Bratisl. Lek. Listy. **34**:612, 1954. Translation by Z. Hrubec available in the library of the Graduate School of Public Health, University of Pittsburgh.

VOL.
5
1957

THE AGGLUTINATION REACTION IN RHEUMATOID ARTHRITIS

MORRIS ZIFF, PH.D., M.D.

NEW YORK, N. Y.

From the Study Group on Rheumatic Diseases, and the Department of Medicine, New York University College of Medicine

(Received for publication Feb. 5, 1957.)

THE capacity of the serum of patients with rheumatoid arthritis to agglutinate sensitized particulate bodies has been demonstrated with bacteria, erythrocytes, collodion particles, and latex particles. This property is probably dependent in all instances on the presence in the serum of the same factor (or perhaps closely related factors), the presence of which is, with certain uncommon exceptions, unique to the serum of patients with rheumatoid arthritis. It is rarely found in other arthritides which closely resemble rheumatoid arthritis both clinically and pathologically, and its concentration in rheumatoid serum is largely uninfluenced by the activity of the disease. By sensitive methods, it has been possible to demonstrate this factor in almost all patients with rheumatoid arthritis. Thus, the elaboration of a "rheumatoid factor" appears in some unknown, but, nevertheless, fundamental manner, to be related to the rheumatoid process. It has received increasing study in recent years not only as a diagnostic aid, but more importantly as a possible clue to information about the etiology and pathogenesis of the disease.

EARLY AGGLUTINATION SYSTEMS

Streptococcal Agglutination.—Agglutination by sera of patients with rheumatoid arthritis was first observed in 1930 when Cecil, Nicholls, and Stainsby[1] reported that such sera agglutinated certain strains of streptococci. It was subsequently shown that group A hemolytic streptococci were agglutinated in higher titer than were other strains tested.[2] In addition to group A streptococci, however, nonencapsulated pneumococci,[3,4] enterococci,[5] and *Staphylococcus aureus*[6] were also agglutinated. The diversity of organisms which were agglutinated suggested that the agglutinating activity of rheumatoid sera was not due to specific bacterial agglutinins but rather to a nonspecific agglutinating factor.

Although some investigators studied the agglutination of hemolytic streptococci as a diagnostic procedure for rheumatoid arthritis with encouraging results,[7,8] this test has not proved to be generally useful. The need to work

The author wishes to acknowledge the contributions of Ina Rubenstein, B.A., in the compilation of the data and preparation of the manuscript.

with a number of strains of streptococci simultaneously, the occurrence of doubtful agglutination, and the necessity for rigid controls made the procedure technically difficult. This, combined with a low incidence of positive tests, i.e., of the order of 50 per cent,[9-12] has resulted in abandonment of this procedure generally.

Collodion Particle Agglutination.—In 1946, Wallis[13,14] observed that a number of rheumatoid sera agglutinated not only hemolytic streptococci and pneumococci, but also collodion particles. This was not true of most normal sera tested. A relationship between collodion particle agglutination and streptococcal agglutination was demonstrated by the fact that the agglutinating activity of rheumatoid sera toward the collodion particle was consistently reduced by prior absorption with the hemolytic streptococcus. Similarly, the agglutination titer against the streptococcus was reduced by absorption with collodion particles. The significance of this work lies in the fact that it emphasized the nonspecificity of the particulate body in the agglutinating system and stimulated later attempts to use other inert particles to carry out the agglutination reaction.

VOL.
5
1957

HEMAGGLUTINATION

Differential Agglutination Test.—In 1912, Dean[15] demonstrated that the globulin fraction of normal guinea pig serum contained a thermostable substance which agglutinated sheep erythrocytes sensitized with small amounts of homologous amboceptor (rabbit anti-sheep cell serum).

Although the capacity of certain human sera to agglutinate red blood cells sensitized with homologous amboceptor had been previously reported,[16] it was Waaler who, in 1940, first called attention to the capacity of rheumatoid sera to agglutinate sensitized red cells. In the course of routine studies of complement fixation, Waaler[17] found that it was possible to effect a marked increase in the agglutinating titer of rabbit amboceptor for sheep cells by addition of a small amount of rheumatoid serum. He found "agglutination activating activity" in 35 per cent of rheumatoid sera tested, while control sera had only weak activity (Table I).

In 1948, attention was again drawn to the hemagglutination phenomenon by Rose, Ragan, Pearce, and Lipman.[18] Their work marked the beginning of efforts to utilize agglutination of sensitized red cells as a diagnostic procedure. Sera were heated to inactivate complement, which would interfere by inducing hemolysis in the presence of amboceptor. Sheep cells were sensitized with a subagglutinating dose of amboceptor, and sera then tested in dilution against the sensitized cells.

Human serum contains a heterophile antibody which agglutinates sheep cells.[19] To correct for the presence of this antibody, the titer of test sera against unsensitized cells was also determined and the result of the test recorded as the quotient of the titers against sensitized cells and unsensitized cells. When this differential titer was 16 or greater, the test was regarded as positive. By this procedure, between 30 and 65 per cent of patients with peripheral rheumatoid arthritis have given positive tests[9,17,18,22-26] (Table I).

It should be pointed out that the type of sensitization used by the investigators listed in Table I varied greatly. In some cases it was based on the hemolytic titer of the amboceptor and in others on the agglutinating titer. Use of the hemolytic titer of amboceptor has not been as satisfactory as that of the agglutinating titer, since hemolysis plays no part in the reaction, and the hemolytic titer is not necessarily related directly to the agglutination titer.[20,21] In later procedures to be described, the more logical practice of basing the dilution of amboceptor on its agglutinating titer was adopted.

TABLE I. RESULTS OF DIFFERENTIAL SHEEP CELL AGGLUTINATION TEST IN RHEUMATOID AND CONTROL SUBJECTS

AUTHOR	RHEUMATOID ARTHRITIS			CONTROLS*	
	ACTIVITY	NUMBER OF PATIENTS	PER CENT POSITIVE	NUMBER OF PATIENTS	PER CENT POSITIVE
Waaler[17] 1940	†	77	35	202‡	4.9
Rose et al.[18] 1948	Active Inactive	27 16	100 50	67	3
Brown et al.[9] 1949	Active Inactive	62 20	55 30	83	1
Sulkin et al.[22] 1949	†	35	46	113	1
Miller et al.[23] 1949	Active	21	67	23§	30
Jawetz and Hook[24] 1949	Active Inactive	57 21	32 0	82	1
Wager[25] 1950	†	221	59	1049	5.1
Scott[26] 1952	†	124	61	172	7.6

*Includes normal individuals and patients with both rheumatic and nonrheumatic diseases.
†Activity not specified.
‡Does not include patients with joint involvement.
§Includes mainly patients with joint involvement.

Modified Sheep Cell Agglutination Test.—The relatively low incidence of positive tests, especially in early cases[9] and in mild cases[22,23] led to disappointment in the Waaler-Rose test as a diagnostic procedure. Efforts were soon made to simplify the method and increase its sensitivity. Jawetz and Hook[24] attempted to absorb the heterophile antibody using beef erythrocytes or guinea pig kidney. Subsequently, Heller, Jacobson, and Kolodny,[27] Ball,[28] and Svartz[29] introduced the modification of absorbing heterophile antibody with packed sheep erythrocytes. Thus, it became possible to dispense with differential agglutination, the titer being read directly against sensitized cells.

It was found by Heller and co-workers[27] that sera of 94 per cent of patients with active peripheral rheumatoid arthritis (Table II) and 70 per cent of an over-all group of active and inactive patients showed significant titers. Similar results were reported by Svartz and Schlossmann[29,30] and Alexander and de Forest.[31] Ball[28,32] concluded, however, that the modified test was not as sensitive as found by previous investigators. On the basis of tests in 642 patients with rheumatoid arthritis, he found that only 48 per cent of the active cases and 25 per cent of the inactive cases gave positive tests. In 1,301 control cases, positive results were obtained in 2.5 per cent (Table II).

TABLE II. RESULTS OF SENSITIZED SHEEP CELL AGGLUTINATION TEST ON ABSORBED SERA IN RHEUMATOID AND CONTROL SUBJECTS

AUTHOR	RHEUMATOID ARTHRITIS		CONTROLS*	
	NUMBER OF PATIENTS	PER CENT POSITIVE	NUMBER OF PATIENTS	PER CENT POSITIVE
Heller et al.[27] 1949	31 (Active) 15 (Inact.)	94 7	111	2
Pike et al.[90] 1950	159	62	98	1.1
Hobson and Gorill[40] 1952	67	85	68	13
Winblad[49] 1952	314	49	1032	5.6
Svartz and Schlossmann[30] 1952	312	90	185†	4.9
Ball[32] 1952	642	44	1301	2.5
de Forest et al.[48] 1956	121	94	244	4.5

*Includes normal individuals and patients with both rheumatic and nonrheumatic diseases.
†Includes only patients without joint or musculoskeletal involvement.

Several groups have compared the differential and modified agglutination tests in the same patients. It was found by Heller[27] that 11 of 39 patients in whom the Waaler-Rose test was negative gave positive results by the modified method. No sera were encountered in which the Waaler-Rose test was positive and the modified test negative. Pike, Sulkin and Coggeshall,[33] and Scott[26] have also reported increases in sensitivity with the modified test.

Animal Serum Potentiated Agglutination.—In 1952, Heller and co-workers[34] and Winblad[21] showed that the addition of certain animal sera to rheumatoid serum resulted in a potentiation of the agglutinating activity of the rheumatoid serum. The most potent animal serum in this respect was sheep serum. Accordingly, test sera were diluted with saline on the one hand, and dilute sheep serum on the other, and added to lightly sensitized sheep erythrocytes. It was found

that 85 per cent of the rheumatoid sera tested showed a fourfold or greater increase in titer when diluted with sheep serum diluent instead of saline, while only 1.6 per cent of control sera did the same.[34] An increase in titer of this magnitude was adopted as evidence of a positive test (S.E.A. test, Table III). In a later publication, Jacobson and associates[35] found a smaller incidence of positive results using this method, reporting positive results in 62 per cent of 331 patients with rheumatoid arthritis.

TABLE III. RESULTS OF RECENT MODIFICATIONS OF THE AGGLUTINATION TEST IN RHEUMATOID AND CONTROL SERA

AUTHOR	TEST	RTD. ARTHRITIS		CONTROLS*	
		NUMBER PATIENTS	PER CENT POSITIVE	NUMBER PATIENTS	PER CENT POSITIVE
Heller et al.[34] 1952	S.E.A.	114	85	245	1.6
Svartz and Schlossmann[36] 1954	Cold globulin	100	95	100	10
Jacobson et al.[35] 1956	S.E.A. F II	331 180	62 69	560† 376†	3 2
Ziff et al.[37,54] 1956	Euglobulin agglutination Euglobulin inhibition	131 127	89 98	187 166	3 4
Hess[39] 1956	Euglobulin fraction	70	91	80	6
Craig et al.[38] 1956	Euglobulin fraction	151	86	114†	1
Plotz and Singer[48] 1956	Latex particle	150	71	1230	3

*Includes normal individuals and patients with rheumatic and nonrheumatic diseases.
†Does not include patients with joint involvement.

Animal serum potentiation, though of considerable interest from a theoretical point of view, did not provide a significant advance in sensitivity. It had the additional disadvantage of requiring two sets of dilutions, and also introduced a new variable into the procedure in the form of an animal serum diluent.

Agglutination Tests on the Globulin Fraction.—Recently three groups have carried out the sensitized sheep cell agglutination test on globulin fractions.[36-38] Svartz and Schlossmann[36] utilized the cold globulin fraction of serum, prepared by diluting the absorbed serum with 14 volumes of water and allowing it to stand in the cold. The agglutination titer of the cold precipitable fraction was then determined by standard techniques. A significant titer was reported in 95 per cent of patients with rheumatoid arthritis.

The euglobulin fraction of serum has been tested by Ziff and associates[37] (Table III). This fraction was prepared by dialysis against dilute citrate-phosphate buffer at pH 5.8 and tested for agglutinating activity against sheep cells sensitized in the usual manner with amboceptor, but to a relatively high degree, i.e., one-half the basic agglutinating titer (B.A.T.). About 90 per cent

of patients with rheumatoid arthritis showed significant agglutinating activity. This has recently been confirmed by Hess.[39] The incidence of positive tests carried out simultaneously[37] on whole serum by the procedure of Heller and his co-workers[34] and by a modified Waaler-Rose technique,[40] and on the cold globulin fraction[36] was smaller.

In nonrheumatoid patients, the incidence of false positive tests in one series, using the euglobulin fraction, was 1.9 per cent.[37] Using whole serum, however, at the high degree of sensitization employed (½ B.A.T.), there were 13 per cent false positive tests in the same patients. The same incidence of false positive tests with whole serum was observed by Hobson and Gorill[40] at this level of sensitization (Table II), and an even higher percentage was noted by Bernstock, Bedson, and Glyn.[41] It appeared, therefore, that testing of the euglobulin fraction made it possible, by sensitizing strongly, to obtain an increase in sensitivity without increasing false positive reactions. This would suggest that precipitation of euglobulin eliminated a factor present, at least in some nonrheumatoid sera, in sufficient concentration to agglutinate highly sensitized sheep erythrocytes.

Craig, Kerby, and Persons[38] have precipitated the euglobulin fraction rapidly by dilution of serum with nine volumes of 0.0027 N hydrochloric acid according to the method of Erickson and co-workers.[42] The resulting precipitate was tested as described by Ziff and co-workers.[37] Eighty-six per cent of 151 patients with unequivocal rheumatoid arthritis and one per cent of control subjects with no evident joint disease gave positive tests.

Ziff and his associates[37] have studied the inhibition of agglutination of sensitized sheep cells by the euglobulin fraction, and described a sensitive procedure, which will be discussed below, for detecting the presence of the agglutinating factor.

F II Test.—Winblad[21] observed that diluted rabbit serum added to a system containing sensitized sheep cells and rheumatoid serum inhibited agglutination at carefully adjusted concentrations of rabbit serum and sensitizing amboceptor. Subsequently Heller and co-workers[43] established that some human sera exerted the same effect. The inhibitory substance was found to be present entirely in fraction II, the gamma globulin fraction. It was postulated that the gamma globulin had an affinity for the rheumatoid factor and inhibited agglutination by engaging in competition with the sensitized sheep cell for this factor. This suggested that a test might be developed on the basis of the affinity of human gamma globulin for the rheumatoid factor using fraction II as the sensitizing agent. Accordingly, sheep red cells were treated with a dilute solution of tannic acid by the method of Boyden,[44] thus rendering them capable of adsorbing gamma globulin. The fraction II solution used for sensitization in this procedure was prepared from the lyophilized powder derived from pooled human plasma. The test was read from the patterns of the agglutinated cells, following incubation with diluted serum samples. The incidence of positive tests in patients with rheumatoid arthritis was 69 per cent.[35]

The F II test has the advantages that the reagents are readily standardized, and that agglutination is easily read. When the test is positive, the titer is usually high so that accurate determination of the end point of agglutination is

not critical. It is necessary, however, that sera be inactivated and absorbed as in earlier procedures. Actual testing, following absorption, takes two days and the results are read on the third day. The F II test has not provided the increased sensitivity so sorely needed for diagnosis; nevertheless, for clinical screening it has proved to be a practical and reliable procedure within the limits of its sensitivity.

LATEX PARTICLE FIXATION TEST

The demonstration that sheep erythrocytes treated with tannic acid could be sensitized by human gamma globulin suggested that an essential feature of the agglutination phenomenon was a reaction between a constituent of the gamma globulin adsorbed on the cell surface and the rheumatoid factor.[43] Accordingly, Singer and Plotz[45] investigated the agglutination of polystyrene latex particles in the presence of human gamma globulin. A fine suspension of latex particles was made up in a buffered saline solution of lyophilized human gamma globulin and the mixture was added to dilutions of rheumatoid serum. Following a short incubation period and centrifugation, the resultant visible agglutination was read with the naked eye.

This procedure dispenses with heat inactivation and the laborious process of absorption of test sera. When sera are positive, titers are usually high, as in the F II test, so that the reading of the end point of agglutination is not critical. The entire procedure may be carried out in a matter of hours.

Plotz and Singer[46] have obtained positive results in 71 per cent of patients with rheumatoid arthritis. A sizable portion of the rheumatoid group, therefore, did not give a positive test by this procedure. This method has not yet been evaluated in other laboratories, but preliminary indications are that the latex procedure will offer a simple and rapid method for clinical screening.

INHIBITION TEST

Ziff and associates[37] observed that when the euglobulin fraction of nonrheumatoid sera was added to a properly diluted known positive rheumatoid serum, agglutination was inhibited, but when the same fraction from rheumatoid sera was added, agglutination was not inhibited. The data obtained indicated that, while the euglobulin fraction of all sera contained an inhibitory substance, this fraction of rheumatoid sera contained both the agglutinating and inhibiting factors. Thus, while the inhibitory globulin precipitated from nonrheumatoid sera was free to block agglutination, that obtained from rheumatoid sera was not free to do so because of the neutralizing effect of the rheumatoid factor precipitated with it. The failure of the euglobulin fraction to inhibit agglutination, therefore, signified the presence of the rheumatoid factor in the serum being tested.

The known positive serum to be inhibited was titered against a lightly sensitized sheep cell suspension, and a concentration four times greater than that present at the end point of agglutination was taken for the test. The euglobulin fraction of sera being tested was obtained by dialysis, dissolved in a volume of neutral buffer equivalent to the volume of serum from which it had been precipitated, and added in dilutions to the known positive serum. Inhibition of agglutination by nonrheumatoid euglobulin was usually observed in dilutions of 1:14 or

greater. Absence of inhibition in a dilution of 1:14 or greater was considered as evidence of the presence of the rheumatoid factor.

When 127 patients in varying stages of adult peripheral rheumatoid arthritis were tested in this way, 98 per cent gave positive tests (Table III). The incidence of positive results in a series of patients with other diseases, including other arthritides, was 4 per cent.

The inhibition method, though technically difficult, is a sensitive technique for demonstrating the presence of the rheumatoid factor. Its sensitivity is based upon the fact that amounts of rheumatoid factor which are not adequate to be demonstrated in a direct agglutination test are sufficient, under the test conditions used, to neutralize the quantity of inhibitor present in the euglobulin fraction. Though difficult to adapt for routine use, it has proved valuable for investigative purposes.

VOL.
5
1957

HEMAGGLUTINATION AND ASPECTS OF RHEUMATOID ARTHRITIS

Though it is well established that the rheumatoid factor does not vary in concentration with the lability of an acute phase reactant, interest has centered on the relation of its titer to a number of aspects of rheumatoid arthritis. In a disease in which the diagnosis is uncertain in the early stages, and of necessity based on clinical impression alone, it is difficult to relate results of a laboratory test to actual presence of the disease or its status. Since the incidence of positive tests has been higher in cases of more advanced disease than in early, borderline, or atypical cases, one may well suspect that, at least in part, this higher incidence is due to increased certainty of diagnosis rather than to progression of the disease with time. It must be accepted, also, that the apparent differences in sensitivity of various agglutination procedures as diagnostic aids are dependent to a considerable degree on the inclination of the investigator either to accept or reject the diagnosis of rheumatoid arthritis in individual cases. It is in the light of these problems that the information to be presented should be considered.

Relation to Activity of Disease.—Numerous investigators have concluded, on the basis of limited data, that the incidence of positive tests is higher in patients with active disease than in those in remission.[9,18,22,24,27,32,40,47] In a recent paper, de Forest, Mucci, and Boisvert[48] reported that the hemagglutination test became negative in 10 of 15 patients who experienced "dramatic Grade I clinical remissions."

Scott,[26] on the other hand, concluded from a careful analysis of his data that there was no statistically significant relation between titer and activity. When repeated serum specimens from 54 patients with rheumatoid arthritis were examined by Pike and co-workers[47] over periods up to 29 months, there was no apparent relationship between changes in clinical symptoms and variation in the titer. In the majority of the patients the titer remained unchanged. Similar findings have been reported by Ball[32] and Alexander and de Forest.[31]

On the basis of available data, it appears, therefore, that the relation of agglutination titer to activity is not established. The number of cases studied in most reports has been small, the criteria of activity not clearly defined, and often not distinguished from severity and functional disability. The incidence

of positive tests in inactive patients has been sufficiently high, furthermore, to make it doubtful that there is a direct relationship to activity. It has been a failing of most studies of the relationship of various clinical aspects of the disease to agglutination titer that conclusions have been based on procedures of low sensitivity, unspecified reproducibility, and inherently subject to a one-tube or 100 per cent error of reading.

Effect of Duration and Progression of Disease.—Four groups[9,22,32,35] have found that the incidence of positive tests increases with duration, but this has not been substantiated by four others.[25,26,47,49] The problem of accuracy of diagnosis is almost certainly a factor in this divergence of findings.

There are numerous reports of positive tests early in the disease. In fact, Jacobson and colleagues[35] cite two cases in which a positive test was obtained on the day of onset of the disease in acute form. The author has observed a positive test as early as three weeks after onset; furthermore, 11 of 12 patients studied in the author's clinic in the first six months of their disease gave positive results by the direct euglobulin test, and all gave positive results by the test for inhibition.[37,54] Hess,[39] using the euglobulin fraction for agglutination, has also reported a high incidence of positive tests in cases of less than six months' duration. Ball,[32] using the modified Waaler-Rose procedure, found that 40 per cent of patients in the first six months of their disease gave positive tests.

Relation to Erythrocyte Sedimentation Rate.—Though it is accepted that the level of the rheumatoid factor does not reflect the inflammatory status in the manner of an acute phase reactant, opinions differ as to whether the hemagglutination titer shows a correlation with the erythrocyte sedimentation rate. No correlation was found by five groups of investigators.[9,18,22,26,32] Wager[25] and Winblad,[49] on the other hand, have reported a correlation. This was not consistent in individual cases, however, according to Wager, since the titer was sometimes high in cases with a normal sedimentation rate and vice versa.

Relation to Stage of Disease, Functional Capacity, and X-ray Changes.—Although the relationship of titer to duration of disease is, as mentioned above, not clear-cut, it has, nevertheless, been the common experience that the highest titers tend to occur in the sera of patients whose disease is most pronounced. Jacobson and associates,[35] using both the potentiated serum agglutination test and the F II test, found that patients in Stage I or Class I of the Steinbrocker classification[50] showed a lower incidence of positive tests than patients in more advanced stages or with greater limitation of function. It was observed by Heller's group[27] that the sheep cell test was most frequently positive in patients who had x-ray evidence of small joint involvement, and tended to be negative in patients in whom the x-rays showed no joint involvement. Similarly, Ball[32] has reported that whereas 55 per cent of patients with advanced x-ray changes gave positive tests, only 21 per cent of patients with normal x-ray findings did so.

Relation to Subcutaneous Nodules.—The strikingly increased incidence of positive tests in patients with subcutaneous nodules was first pointed out by Ball.[32] Seventy-eight per cent of his patients with nodules gave positive tests as compared to 39 per cent without. Jacobson and others[35] found that well over 90 per cent of patients with nodules gave positive tests. It was distinctly un-

usual for these authors to obtain a negative reaction in a patient with nodule formation regardless of the apparent stage of the disease.

Relation to Sex.—A number of reports[31,32,35] have indicated that the hemagglutination test is more frequently positive in men. Ball[32] found a 60 per cent incidence of positive tests in men as compared to 38 per cent in women. This relationship has been denied by Scott.[26]

Effect of Therapy.—Data on the effect of therapy on the hemagglutination titer are meager. Svartz and Schlossmann[29] in 6 patients, and Hobson and Gorill[40] in 8 patients, observed no effect on the titer as a result of corticotropin or cortisone therapy. These impressions, however, were based upon brief periods of treatment. In a number of cases treated with gold salts and in 9 patients treated with corticotropin or cortisone, Ball[32] found that there was no change in the result of the test whether the patient went into remission or not. In those cases in which the reaction changed from positive to negative or vice versa, there seemed to be no correlation with the clinical state. Using cortisone, corticotropin, gold, and supportive measures, Pike, Sulkin, Coggeshall, and Burdette[47] noted no change in titer, and de Forest and Alexander[31] saw no change in titer in a few patients after extended periods of treatment with cortisone and gold, although significant clinical improvement occurred. Jacobson and colleagues,[35] in a larger group of patients, found "insignificant changes in titer and few instances of conversion of positive to negative (or vice versa) with any grade of response to therapy," which included adequate amounts of gold salts or prolonged periods of hormonal and salicylate therapy.

Discussion.—It would appear that the more pronounced the total development of the disease the more likely is the hemagglutination test to be positive. The results are especially well correlated with the presence of x-ray changes and subcutaneous nodules. Opinion is divided as to whether the titer is related to duration of disease and to the erythrocyte sedimentation rate; and the relationship to activity, often claimed, has not been convincingly proved. It is commonly but not universally agreed that once positive, the test tends to remain positive regardless of therapy and changes in activity of the disease. Thus, the elaboration of the rheumatoid factor seems to be more closely associated with the deep-seated, anatomic changes of rheumatoid arthritis rather than with the purely inflammatory or fluctuating aspects of the disease.

The rheumatoid factor has been demonstrated frequently in the early stages of the disease. By the inhibition procedure, it has been found in practically all patients regardless of the stage of the disease. It would appear, therefore, that the presence of this factor is an essential feature of the rheumatoid process and that the difficulty of demonstrating it in certain patients is a consequence of the lack of sensitivity of available tests.

AGGLUTINATION REACTION IN OTHER RHEUMATIC DISEASES

Ankylosing Spondylitis.—Of 456 cases of ankylosing spondylitis reported in the literature in which the presence of peripheral joint involvement was not specified, 12 gave positive tests, an incidence of 2.6 per cent (Table IV). When peripheral joint involvement was specified as being present, positive tests were

VOL.
5
1957

given by 9 of 48 patients, or 19 per cent. It is not clear what proportion of the small group with positive tests had typical ankylosing spondylitis with peripheral spread, and what proportion had atypical spondylitis beginning as rheumatoid arthritis.[52]

TABLE IV. RESULTS OF SENSITIZED SHEEP CELL AGGLUTINATION TESTS IN VARIOUS DISEASES

DISEASE	REFERENCES	NUMBER OF PATIENTS	NUMBER POSITIVE	PER CENT POSITIVE
Juvenile rheumatoid arthritis	18, 22, 26, 31, 32, 37, 54	69	26	38
Disseminated lupus erythematosus	18, 22, 23, 26, 30-32, 35-37, 49, 55	83	28	34
Scleroderma	22, 30-32, 35, 49, 54	25	7	28
Polyarteritis nodosa	31, 32, 35, 36, 49, 54	14	3	21
Ankylosing spondylitis with peripheral joint involvement	18 22, 23, 27, 35, 37, 49, 51	48	9	19
Infectious hepatitis	22, 24, 26, 27, 30, 36	43	7	16
Dermatomyositis	18, 31, 32, 35, 54	8	1	12
Palindromic rheumatism	35, 54	8	1	12
Psoriasis with arthritis	27, 31, 32, 35, 37, 51	67	7	10
Reiter's syndrome	22, 30, 32, 35, 36, 49, 51	50	5	10
Osteoarthritis	18, 22, 23, 30-32, 35-37, 49	498	29	5.8
Specific infectious arthritis	18, 22, 23, 32, 35, 36	47	2	4.3
Ankylosing spondylitis without peripheral joint involvement	18, 22-24, 27, 30-32, 35-37, 49, 51	456	12	2.6
Rheumatic fever	18, 22-24, 26, 30-32, 36, 37	455	11	2.4
Gout	18, 31, 35, 37	98	1	1.0
Ulcerative colitis with arthritis	35, 51	13	0	0
Psychogenic rheumatism	35	27	0	0
Shoulder-hand syndrome	35	5	0	0

Of 89 patients tested in the author's laboratory, only one gave a positive test.[51] Eleven of these patients, who had peripheral joint involvement, gave negative tests. Only one of approximately 100 patients with ankylosing spondylitis reported by Blumberg and Ragan,[53] of whom 30 per cent had peripheral joint involvement, gave a positive Waaler-Rose test.

The low incidence of positive tests in ankylosing spondylitis, even in the presence of peripheral joint involvement, suggests that peripheral rheumatoid arthritis and ankylosing spondylitis are divergent diseases.

Juvenile Rheumatoid Arthritis.—Results of 69 cases of this disease have been reported, with 26 positive tests, an over-all incidence of 38 per cent (Table IV). In the author's clinic, 12 of 20 patients (60 per cent) gave positive tests with the euglobulin fraction directly, and all gave positive tests when the inhibition procedure was used.[54] In view of the latter results, it would appear that the low incidence of positive tests usually observed in the juvenile disease is attributable to the lack of sensitivity of the procedures employed rather than to absence of the rheumatoid factor. Since in most respects the juvenile and adult forms of the disease are identical, it is to be expected that with more sensitive procedures the rheumatoid factor will be demonstrated in juvenile patients in higher incidence than heretofore.

Psoriasis and Arthritis.—Most authors have not distinguished between psoriatic arthropathy and coincidental psoriasis and rheumatoid arthritis in reporting results of agglutination tests. Tests in 67 patients have been reported; of these, 7 gave positive tests (Table IV). Jacobson and co-workers,[35] who reported positive tests in approximately 20 per cent of such patients, found no difference in results whether or not terminal, interphalangeal joint involvement was present. In the author's clinic, none of 21 patients have given positive tests, even though more than half of these fulfilled the criteria for the diagnosis of coincidental rheumatoid arthritis and psoriasis.

It is apparent that the agglutination test has usually been negative in patients with psoriasis and arthritis. The fact that negative results have been obtained regardless of whether the clinical diagnosis was psoriatic arthropathy or rheumatoid arthritis with psoriasis raises doubt as to whether this distinction is justified. The evidence from agglutination data appears to favor the point of view that, regardless of clinical features, the arthritis which occurs with psoriasis is, in nearly all cases, not typical rheumatoid arthritis.

Disseminated Lupus Erythematosus.—Next to classical rheumatoid arthritis, patients with disseminated lupus erythematosus have shown the highest incidence of positive agglutination tests. Of 83 patients with this disease, 28 (34 per cent) gave positive results (Table IV).

In the author's laboratory, sensitized sheep cell agglutination tests were performed in 18 patients with disseminated lupus erythematosus, all of whom had some form of joint involvement in the course of their disease.[55] Five patients in this group gave positive tests by the inhibitor-block technique, an incidence of 28 per cent. It is significant that the patients who gave positive tests fell into the group which had had either a prolonged history of joint involvement or chronic arthritis resembling that seen in rheumatoid arthritis.

In recent years, the distinction between rheumatoid arthritis and disseminated lupus erythematosus has become less definite. Many patients presenting the clinical picture of rheumatoid arthritis have shown positive L.E. cell tests. In my clinic, for example, 7 of 59 patients with classical rheumatoid arthritis showed positive L.E. tests, an incidence of 12 per cent.[51] Similar results have been reported by others. It is of interest, therefore, that patients with the clinical diagnosis of disseminated lupus erythematosus should show a high incidence of positive agglutination tests, emphasizing the overlap of the two diseases from the other direction.

Other Collagen Diseases.—Positive results have been reported in 7 of 25 cases of scleroderma, 3 of 14 cases of polyarteritis nodosa, and 1 of 8 cases of dermatomyositis (Table IV). The limited number of cases studied thus far in these groups would tend to magnify errors resulting from unwitting inclusion of cases of rheumatoid arthritis. Nevertheless, present data suggest an increased incidence of positive tests in scleroderma and perhaps in polyarteritis nodosa.

Miscellaneous Diseases.—Sera of patients with rheumatic fever, gout, osteoarthritis, specific infectious arthritis, shoulder-hand syndrome, and psychogenic rheumatism have almost uniformly shown negative tests (Table IV). None of 13 cases of ulcerative colitis with arthritis, and only 1 of 8 cases of palindromic rheumatism gave positive tests. Positive results have been reported in 5 of 50 reported cases of Reiter's syndrome and chronic postvenereal arthritis. Here, as in the collagen diseases, the number of cases reported is small, and the apparent small increase in incidence of positive tests may well be due to the inclusion of cases of rheumatoid arthritis.

Among the nonrheumatic diseases, it is worthy of note that sera of 7 patients of 43 with infectious hepatitis yielded positive results, an incidence of 16 per cent. This is relatively high as compared to results in the general population. The possibility exists that in the presence of liver disease abnormal globulins are synthesized which have agglutinating activity.

Discussion.—Positive agglutination tests occur no more frequently in rheumatic fever, gout, osteoarthritis, and specific infectious arthritis than in the general population. In contrast to rheumatoid arthritis, the sensitized sheep cell agglutination reaction is also usually negative in a group of arthritic diseases which resemble it both clinically and pathologically. These include ankylosing spondylitis and the arthritides associated with psoriasis, urethritis, ulcerative colitis, and perhaps also the arthritis that accompanies agammaglobulinemia.[56] In disseminated lupus erythematosus, patients with a significant degree of arthritis frequently show positive tests.

The results presented strongly suggest that ankylosing spondylitis and peripheral rheumatoid arthritis are divergent diseases, and that the distinction commonly made between psoriatic arthropathy and coincidental rheumatoid arthritis and psoriasis is not justified.

Perhaps most important of all, however, the question is raised as to why one variety of chronic synovitis is associated with a characteristic and presumably abnormal serum constituent, while others resembling it, as far as we know, are not.

NATURE OF THE AGGLUTINATION REACTION

The agglutinating property of rheumatoid serum has been demonstrated, as noted previously, with a number of particulate systems, i.e., erythrocytes, bacteria, collodion particles, and latex particles. It is reasonable to assume that the same or closely related agglutinating factors are operative in all these systems. Presumably, in every case the particulate body is coated with a sensitizing factor, which varies for each system. In the classical sensitized sheep cell agglutination reaction (Table V and Fig. 1) the coating factor is rabbit anti-sheep cell antibody. Other antibody sensitized red cell systems have been utilized. Foz and

associates[57] and Pike and his co-workers,[58] have employed human group O cells coated with rabbit antiserum to type O cells (Table V and Fig. 1). Rh-positive cells sensitized with anti-Rh antibody[59,60,91] and human group A cells sensitized with rabbit anti-group-A-substance antibody have also been employed.[61]

Greenbury[61] has recently sensitized sheep erythrocytes by coating them first with the capsular polysaccharide of *Bacterium pneumoniae* type B and subsequently exposing them to a subagglutinating dose of rabbit antiserum against whole *Bact. pneumoniae*. In this case the sensitizing antibody globulin was fixed to the red cell by preliminary treatment with its antigen.

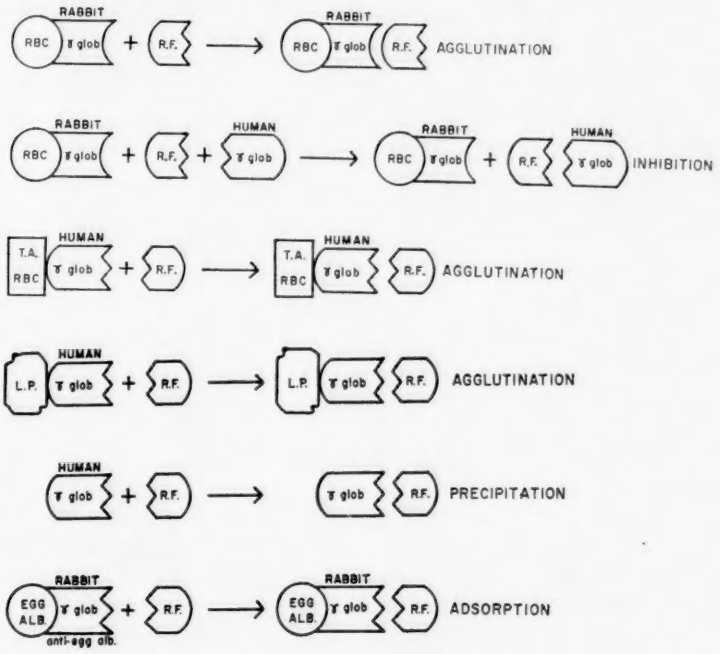

Fig. 1.—Mechanisms of agglutination and inhibition in different systems. *RBC*, sheep red blood cell; *T.A.*, tannic acid treated red blood cell; *L.P.*, latex particle; *R.F.*, rheumatoid factor.

When red cells are treated with tannic acid, their surface properties are so altered that they may be coated with proteins which are not antibodies to them.[44] In this way, Heller's group[43] sensitized tannic acid treated cells with human fraction II with the result that they were strongly agglutinated by rheumatoid serum. This observation in turn led to an interesting finding by Singer and Plotz[45] who were able to "sensitize" polystyrene latex particles with human fraction II so that these, too, were agglutinated or flocculated by rheumatoid sera. These observations emphasize the minor role of the particulate body in the agglutination phenomenon, and provide evidence that the rheumatoid factor does not function inherently as an accessory agglutinating factor to systems in which particulate antigens are agglutinated by their antibodies as postulated by Wager.[25]

Agglutination of bacteria, also, appears to require prior sensitization. Brucella organisms were agglutinated by rheumatoid sera if sensitized with incomplete brucella antibodies.[62] That a sensitizing factor is concerned in the agglutination of beta hemolytic streptococci is apparent from the experiments of Lamont-Havers,[63] who showed that, in addition to an agglutinating factor which precipitated in the cold globulin fraction of rheumatoid serum, a second factor, remaining in the supernatant, was necessary for streptococcal agglutination. The second factor was nonspecific in that it was also found in normal serum. It is likely, by analogy with other agglutinating systems, that this nonspecific factor is a streptococcal antibody which serves as the sensitizing agent. That it is a globulin is suggested by the fact that it is precipitable by dialysis against water.

TABLE V. AGGLUTINATION SYSTEMS

PARTICULATE BODY	SENSITIZING GLOBULIN
1. Sheep erythrocyte	Rabbit amboceptor
2. Human Rh^+ erythrocyte	Human anti-Rh antibody
3. Human group O erythrocyte	Rabbit anti-O cell antibody
4. Human group A erythrocyte	Rabbit anti-group A-substance antibody
5. Sheep erythrocyte coated with *Bact. pneumoniae* polysaccharide	Rabbit anti-*Bact. pneumoniae* polysaccharide antibody
6. Tanned sheep erythrocyte	Human fraction II
7. Latex particle	Human fraction II
8. Brucella bacillus	Incomplete brucella antibody
9. β-hemolytic streptococcus	(Streptococcal antibody)
10. Egg albumin-anti-egg albumin precipitate*	Rabbit anti-egg albumin antibody

*Adsorbs rheumatoid factor, but is not an agglutinating system.

The capacity of the rheumatoid factor to interact with particulate systems in which the sensitizing factor is a fixed gamma globulin, commonly antibody in character, suggests that antigen-antibody precipitates should also combine with this factor. Evidence for this type of reaction is available from two sources.[64,65] Wallis[64] showed that rheumatoid sera precipitated more strongly than controls with extracts of group A hemolytic streptococci and with the C-carbohydrate of this organism. This was attributed to a nonspecific enhancing effect of rheumatoid serum on antigen-antibody precipitation.

Vaughan[65] found that the antigen-antibody complexes in 2 of 5 precipitating systems investigated, i.e., egg albumin-rabbit anti-egg albumin and conalbumin-rabbit anti-conalbumin, absorbed significant amounts of protein-containing material from rheumatoid serum and not from normal serum. There was simultaneously a progressive fall in the sensitized sheep cell agglutination titer, indicating absorption of the rheumatoid factor. The observations of Vaughan are of interest, in that they correspond with accumulated experience that the rheumatoid factor reacts with particulate systems containing gamma globulin, in this case rabbit antibody.

As shown in Table V and Fig. 1, the sensitizing agents for the various agglutination and adsorption systems listed are in each instance gamma globulin constituents. In some cases they are antibodies, but their antibody character ap-

pears to be necessary only for attachment to the particulate body, which itself appears to play a minor role. It would appear, therefore, that the underlying reaction in all cases is one in which the rheumatoid factor reacts with a constituent of the gamma globulin fraction. The gamma globulin constituent is not specific since any one of a number of rabbit and human antibodies to a variety of antigens, as well as fraction II of human plasma, may serve as sensitizing agents.

In the light of the above, it would appear that the phenomenon of inhibition of sensitized sheep cell agglutination[20,37,48] is due to a competition for the rheumatoid factor between amboceptor on the sheep red cell and inhibiting gamma globulin added to the system either in the form of whole serum or its euglobulin fraction (Fig. 1). The inhibiting globulin, present in excess, presumably reacts with the rheumatoid factor preferentially, thereby blocking reaction of the latter with the amboceptor.

VOL.
5
957

The observations presented suggest that it should be possible to demonstrate interaction between fraction II and the rheumatoid factor directly. Since rheumatoid serum contains both these components, it might be expected that such serum would show spontaneous precipitation because of this interaction. It is not surprising, therefore, that a number of workers[13,66,67] have called attention to the fact that saline diluted rheumatoid sera do form visible precipitates on standing.

Williams and co-workers[68] first showed evidence of reaction between fraction II and the rheumatoid factor by demonstrating adsorption of fraction II protein by a euglobulin precipitate from rheumatoid serum. Epstein, Johnson, and Ragan[69] subsequently furnished highly convincing evidence of reaction between the rheumatoid factor and a serum gamma globulin by demonstrating precipitation between fraction II and diluted rheumatoid serum or euglobulin. The data in this preliminary report indicated an equivalence zone of precipitation, suggesting that the reaction had the characteristics of a single antigen-antibody system in which the rheumatoid factor functioned as the antibody. A later report by these authors[70] indicated, however, that the character of the precipitin curve varied with the samples of fraction II and rheumatoid serum employed. There was no consistent relationship between the shape of the curve and the amounts of rheumatoid factor remaining in the supernatant following precipitation, nor was there in most cases a characteristic equivalence point as is usually observed in true antigen-antibody reactions.

With regard to the possible antibody nature of the rheumatoid factor, Foz and Batalla[62] have called attention to the similar properties of Coombs serum and Waaler-Rose positive rheumatoid serum by demonstrating that both agglutinated brucella organisms sensitized with anti-brucella incomplete human antibodies and also Rh-positive erythrocytes sensitized with incomplete human anti-Rh antibodies.[59] They suggested, on this basis, that the rheumatoid factor acted as an autoantibody to the patient's own globulin, altered in some unknown way so as to become "autoantigenic."

Is the rheumatoid factor a true autoantibody? The precipitin data described by Epstein and co-workers do not clearly establish this point of view. Preliminary

evidence indicates that the precipitating activity of fraction II is dependent upon alteration of the protein constituent involved.[71,72] Increased precipitating activity could be produced by heating or by preliminary exposure to an acid pH, suggesting that the precipitation of the rheumatoid factor by fraction II depends to a considerable extent on a decrease in solubility of the precipitating constituent of this fraction.

In the author's opinion, present evidence permits only the conclusion that rheumatoid serum contains one or more substances which combine with a constituent of the gamma globulin fraction, especially if the latter has been altered beforehand either by exposure to heat or acid or by combination with a particulate body. Whether separate rheumatoid factors are concerned with the agglutination of antibody sensitized systems, as exemplified by sensitized sheep cells and F II sensitized systems, remains unclear.

RELATION TO STREPTOCOCCAL AGGLUTINATION

Although the phenomena of streptococcal agglutination and sensitized sheep cell agglutination have usually been demonstrable in the same sera[9,18,25] it has been denied by Waaler[17] and Pike with others[73] that the same factor was involved in both. The latter investigators as well as Lamont-Havers[63] and Thulin[74,75] absorbed rheumatoid sera with streptococci with resultant loss of streptococcal agglutinating activity, but with no decrease in sensitized sheep cell agglutinating capacity. Thulin also showed that L and O streptococcal agglutinating factors of rheumatoid serum migrated more slowly than the hemagglutinating factor on paper electrophoresis, and that treatment of rheumatoid sera with CO_2 precipitated hemagglutinating factor and not streptococcal agglutinating factor. He argued from these data that the sensitized sheep cell factor and the streptococcal agglutinating factor were different substances. Wager[25] has shown, however, that the loss of streptococcal agglutinating activity following absorption with streptococci is due to removal of streptococcal antibody rather than the streptococcal agglutinating factor. This would also follow from the work of Lamont-Havers,[63] reviewed above, who demonstrated that two factors were involved in streptococcal agglutination.

It is possible, therefore, to reconcile the results of Thulin with the point of view that the same factor in rheumatoid serum is responsible for both streptococcal and hemagglutination by the assumption that the differences noted by him were due to the separation of streptococcal antibody from the rheumatoid factor. The similarity of streptococcal agglutination to brucella agglutination, described above, also makes it likely that streptococci and sensitized sheep cells are agglutinated by the same factor.

CONSTITUTION OF THE RHEUMATOID FACTOR

Using salt fractionation, Waaler[17] found the agglutinating activity of rheumatoid serum in the globulin fraction. Rose and associates[18] found all such activity in the electrophoretically separated beta-gamma globulin fraction. When whole serum was examined by paper electrophoresis, the activity migrated in the beta globulin as well as in the faster portions of the gamma globulin.[74]

The hemagglutinating activity of serum fractions separated by alcohol fractionation was determined by Heller's group.[76] All of the activity was found in a fraction, designated by these authors (using the method of Deutsch et al.[77]) as fraction III, which contained albumin, 4.9; alpha globulin, 14.6; beta globulin, 73.1; and gamma globulin, 7.4 per cent. Since other Cohn-Deutsch fractions containing larger amounts of albumin, alpha and gamma globulin were inactive, it was assumed that the rheumatoid factor was associated with the beta-lipoprotein fraction. A similar conclusion was reached by Wager and Alameri[78] following alcohol fractionation. Since it is quite possible that the activity was present in the small but measurable amounts of gamma globulin known to be present in the fractions separated by these investigators, this conclusion is not necessarily correct. On sodium sulfate fractionation,[79] the agglutinating activity was precipitated most consistently in a fraction rich in beta globulin, but the same criticism may apply here, too.

VOL.
5
1957

The agglutinating factor was precipitated in the cold globulin fraction.[36] On zone electrophoresis of the cold globulin precipitate on starch columns, the agglutinating activity was found in the gamma globulin fraction.[80] It also migrated electrophoretically on paper as a gamma globulin component when precipitated by dilution with water.[63]

The discrepancies between the results obtained above on electrophoresis of whole serum and those obtained on purified fractions by the latter two investigators suggest that in whole serum the rheumatoid factor interacts with faster moving proteins which raise its mobility, while in fractions containing only gamma globulin it remains with this fraction.

Rheumatoid serum and its euglobulin fraction have been applied to cellulose ion exchange columns[81,82] by Lospalluto and Ziff,[83] and agglutinating activity has been recovered quantitatively from both anion and cation exchangers. Though the main bulk of the gamma globulin fraction was eluted from the anion exchange column in the first major peak, all of the agglutinating activity was found consistently in a fraction far removed from this peak. The titer per milligram of nitrogen of the active fraction recovered from eluates has varied from 100 to 800 times that of the original serum. Boundary electrophoresis of active eluates has usually shown two main components, both having mobilities in the gamma globulin range. All of the activity was present entirely in the slower component, which in one experiment had a mobility of 7.5×10^{-6} cm.^{2} volt^{-1}sec.$^{-1}$. It appears from these results that the agglutinating factor, as recovered by ion exchange chromatography, is a slow-moving component of the gamma globulin fraction, which separates widely from the main bulk of the gamma globulin on the ion exchanger.

A chromatographically purified fraction, containing all of the agglutinating activity of the serum in 0.6 per cent of the original nitrogen, contained 2.8 per cent hexosamine and 4.3 per cent tryptophane-reacting polysaccharide as compared with 1.9 per cent hexosamine and 2.1 per cent polysaccharide in the original serum. Smyth and Clark[84] have suggested that a polysaccharide component of the globulin fraction is concerned in the agglutination reaction because there was a significant decrease in the polysaccharide content of the medium following agglutination of sensitized sheep cells by the euglobulin fraction.

Agglutinating activity remained after exposure to a temperature of 60° C. for 30 minutes,[20] but was lost at 80° C.[83] Activity persisted after storage for five months in the frozen state, and after repeated freezing and thawing.[20] It was lost at pH 2 after one hour, but not at pH 4.[83] After 24 hours at the latter pH, however, activity disappeared. Removal of lipids by treatment with cold alcohol and ether did not destroy agglutinating activity,[73] nor did repeated extraction with ethyl ether.[76] The agglutinating factor resisted inactivation when the euglobulin fraction was incubated for 24 hours with both papain and trypsin in high concentration.[83] No conclusion could be reached about the stability toward pepsin because of the instability of the factor at the acid pH necessary for pepsin digestion.

Hobson and Gorill[40] have concluded that the properties of the rheumatoid factor closely resemble those of the heat stable fourth component (C′4) of complement. Further evidence for this identification has not been presented, and has, in fact, been denied by Svartz and Schlossmann.[85] In contrast to the finding of Hobson and Gorill, that the agglutinating activity remained in the supernatant following globulin precipitation with CO_2, Svartz and Schlossmann found it in the euglobulin precipitate as well.

Svartz and Schlossmann[80] have grown nonhemolytic cocci, cultured from the throats of patients with rheumatoid arthritis, on a medium containing tendons and periarticular tissue, and from this medium have subsequently precipitated a cold globulin fraction which agglutinated sensitized sheep cells in high titer. The suggestion was made that the agglutinating factor so obtained was elaborated by the action of bacterial enzymes on connective tissue. A number of variables in these preliminary experiments have not as yet been controlled, however. Hemagglutinating activity has also been obtained by these authors in a polysaccharide extract of the granulation tissue of a joint capsule from a patient with rheumatoid arthritis, but details are not given.[29]

IMMUNOLOGIC PROPERTIES OF THE RHEUMATOID FACTOR

Is the rheumatoid factor a new serum constituent, or is it normally occurring but elaborated in greater quantity in rheumatoid serum? Attempts have been made to determine this by investigating whether the factor is antigenic in rabbits, and if so whether the antigen may be found only in rheumatoid serum. Svartz,[86] with Schlossmann, has reported briefly that sera of rabbits injected with rheumatoid serum or joint fluid developed strong agglutination inhibitory activity, presumably due to antibody formation to the rheumatoid factor. Brown,[87] working in the author's laboratory, found that the sera of rabbits immunized with a cold globulin fraction from rheumatoid serum, which had been previously absorbed with euglobulin from normal serum, exhibited marked agglutination inhibitory activity. These antisera gave precipitin reactions with 11 of 14 rheumatoid sera but not with control sera, and showed two extra bands in gel diffusion experiments against rheumatoid sera which were not observed with normal sera. Subsequent attempts by Boettiger, Lospalluto, and Ziff[88] to absorb rabbit antibody to the rheumatoid factor differentially with a variety of globulin preparations have revealed no marked difference in specificity between fractions

from normal and rheumatoid sources, presumably because of cross reaction. It would appear from this that clear-cut evidence of an antigen unique to rheumatoid serum must await sufficient purification of the rheumatoid factor. Because present indications are that this factor is a gamma globulin component, it may well be that even when a purified antigen is available it will be difficult to avoid cross reaction of its antiserum with other gamma globulin.

INHIBITION REACTION

It has been suggested above that inhibition results from a reaction between a fraction II constituent and the rheumatoid factor. There is little knowledge of the chemical nature of the inhibitor. Heller and co-workers[43] established that the inhibitory activity of serum was concentrated in fraction II. It is not known whether the activity is restricted to a single constituent of this fraction or is a characteristic of a group of constituents.

When rheumatoid serum was fractionated by dialysis at varying pH, all of the agglutinating activity was precipitated between pH 6.5 and 7.5, while precipitates obtained below pH 6.5 showed inhibitory activity.[83] Inhibitory activity was found in precipitates from nonrheumatoid sera between pH 6.5 and 7.5 as well as at lower pH. When rheumatoid sera were fractionated with ammonium sulfate, agglutinating activity was precipitated between 1.2 and 1.4 molar concentration, while inhibitor activity was obtained from the same serum over the range 1.2 to 2.0 M. From these results it appears that the agglutinating factor precipitates over a relatively narrow range of pH and salt concentration, while the inhibitor precipitates over a much wider range. This observation suggests that either inhibitory activity is exhibited by a group of proteins or that a single protein is coprecipitated over a wide range of pH and salt concentration. These results also indicate that rheumatoid sera contain both inhibitor and agglutinator.

Evidence that not all gamma globulin is active as inhibitor has been presented by Williams and colleagues,[68] who found that when this fraction was separated by curtain electrophoresis at pH 3.2, the peak of inhibitor activity lay far to the anodic side of the protein concentration maximum. Whether this is due to the formation of altered gamma globulin is not clear.[71,72]

When rheumatoid serum or its euglobulin fraction was chromatographed on cellulose anion exchanger, inhibitory activity was eluted in the first peak, which contained the main bulk of the gamma globulin fraction, while the last peak to be eluted, which was also composed of gamma globulin, contained all of the agglutinating activity.[83]

An interesting type of inhibition has recently been reported by Greenbury.[61] The latter author sensitized sheep erythrocytes by exposing them first to the capsular polysaccharide of *Bact. pneumoniae* type B, and subsequently to rabbit antiserum against whole *Bact. pneumoniae*. Agglutination of these cells by rheumatoid serum could be reversed by addition of excess *Bact. pneumoniae* polysaccharide. A similar reversal of agglutination of human group A cells sensitized by rabbit anti-group-A-substance antibody was effected by addition of excess group-A-substance. The rheumatoid factor in each case was shown to have

been eluted from the cells by this treatment presumably because the excess of antigen to the sensitizing antibody displaced the rheumatoid factor from its point of attachment to this globulin.

A number of simple organic compounds have been shown to have inhibitory activity in the concentration range 10^{-3} to 10^{-4} M.[68] These are glycylglycine, ureidosuccinic acid, and 5-hydantoin acetic acid. Svartz[89] has recently found that acetazolamide (Diamox) has inhibitory activity.

SUMMARY

In the serum of most patients with rheumatoid arthritis and some with other collagen diseases, an agglutinating factor is present. The factor is not detectable with a significant incidence in the serum of patients with other chronic arthritides. A variety of agglutinating systems, including sensitized bacteria, erythrocytes, and synthetic polymers, have been utilized to demonstrate the presence of the rheumatoid factor. It is likely, but not certain, that the same factor is concerned in each system.

The sensitizing agent is, in all instances, a gamma globulin constituent of variable composition attached to the particulate body, in some cases as an antibody and in others nonspecifically. Agglutination is believed to occur as a result of reaction between the sensitizing factor and the rheumatoid factor. The demonstration of precipitation between fraction II (gamma globulin) and rheumatoid serum supports this point of view.

When whole serum is examined electrophoretically, the agglutinating activity is found in the beta and gamma globulin fractions, but when purified fractions are so studied, the activity is usually found in the gamma globulin fraction.

It has been suggested that the rheumatoid factor is an autoantibody to gamma globulin. Though it is well established that interaction occurs between this factor and various gamma globulin constituents, it has not yet been proved that the factor is a true antibody.

One or more constituents of the gamma globulin fraction of human and rabbit serum have the capacity to inhibit the agglutinating activity of the rheumatoid factor when present in sufficient concentration to bind it preferentially.

The presence of an agglutinating factor in the gamma globulin fraction of the serum of patients with rheumatoid arthritis suggests, along with other data, that alterations in the composition of this fraction may play an important part in the pathogenesis of this disease.

REFERENCES

1. Cecil, R. L., Nicholls, E. E., and Stainsby, W. J.: Characteristics of Streptococci Isolated From Patients With Rheumatic Fever and Chronic Infectious Arthritis, Proc. Am. Assoc. Pathologists & Bacteriologists, Am. J. Path. **6**:619, 1930.
2. Dawson, M. H., Olmstead, M., and Boots, R.: Agglutination and Precipitation Reactions in Rheumatoid Arthritis With Hemolytic Streptococci Groups A to G, Proc. Soc. Exper. Biol. & Med. **34**:80, 1936.
3. Dawson, M. H., Olmstead, M., and Boots, R.: Agglutination Reaction With Streptococcus Hemolyticus, J. Immunol. **23**:187, 1932.
4. Wallis, A. D.: Rheumatoid Arthritis. III. The Pneumococcus Antibodies, Am. J. Med. Sc. **212**:718, 1946.
5. Olhagen, B.: In Discussion of Paper by Edstrom, G. and Winblad, S.: Agglutination mot Haemolytiska Streptococcer vid Kronisk Polyarthrit, Nord. med. **33**:509, 1947.

6. Oker-Blom, N.: Om Agglutination av Staphylococcus Aureus vid Kronisk Polyarthrit, Nord. med. **41**:74, 1949.
7. Nicholls, E. E., and Stainsby, W. J.: Streptococcal Agglutinins in Chronic Infectious Arthritis, J. Clin. Invest. **10**:331, 1931.
8. McEwen, C., Bunim, J. J., and Alexander, R. C.: Bacteriologic and Immunologic Studies in Arthritis: II. Results of Various Immunologic Tests in Different Forms of Arthritis, J. Lab. & Clin. Med. **21**:465, 1936.
9. Brown, R., Bunim, J. J., and McEwen, C.: Differential Sheep Cell Agglutination Test in Rheumatoid Arthritis, Ann. Rheumat. Dis. **8**:299, 1949.
10. Short, C. L., Dienes, L., and Bauer, W.: Rheumatoid Arthritis. A Comparative Evaluation of the Commonly Employed Diagnostic Tests, J.A.M.A. **108**:2087, 1937.
11. Nicholls, E. E., and Stainsby, W. J.: Further Studies on the Agglutination Reaction in Chronic Arthritis, J. Clin. Invest. **12**:505, 1933.
12. Boots, R. H., Lipman, M. O., Coss, J. A., and Ragan, C.: Immunologic Reactions in Rheumatoid Arthritis. Proc. Seventh International Congress of Rheumatic Diseases, Philadelphia, 1952, W. B. Saunders Company, p. 336.
13. Wallis, A. D.: Rheumatoid Arthritis. II. Non-Specific Serologic Reactions, Am. J. Med. Sc. **212**:716, 1946.
14. Wallis, A. D.: Rheumatoid Arthritis. V. The Agglutination of Hemolytic Streptococci, Ibid. **213**:94, 1947.
15. Dean, H. R.: On the Factors Concerned in Agglutination. Proc. Roy. Soc. London. Series B, **84**:416, 1912.
16. Meyer, K.: Ueber Hämmagglutininvermehrung und Hämmagglutination fordernde Wirkung bei menschlichen Seren., Ztschr. f. Immunitätsforsch. u. exper. Therap. **34**:229, 1922.
17. Waaler, E.: On the Occurrence of a Factor in Human Serum Activating the Specific Agglutination of Sheep Blood Corpuscles. Acta path. et microbiol. scandinav. **17**:172, 1940.
18. Rose, H. M., Ragan, C., Pearce, E., and Lipman, M. O.: Differential Agglutination of Normal and Sensitized Sheep Erythrocytes by Sera of Patients With Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **68**:1, 1948.
19. Kabat, E. A., and Mayer, M. M.: Experimental Immunochemistry, Springfield, Ill., 1948, Charles C Thomas, p. 135.
20. Pike, R. M., Sulkin, S. E., and Coggeshall, H. C.: Serological Reactions in Rheumatoid Arthritis. I. Factors Affecting the Agglutination of Sensitized Sheep Erythrocytes in Rheumatoid Arthritis Serum, J. Immunol. **63**:441, 1949.
21. Winblad, S.: Studies on Agglutination of Sensitized Sheep Cells in Rheumatic Diseases. II. On the Nature of the Agglutinating Serum Factor, Acta med. scandinav. **142**:458, 1952.
22. Sulkin, S. E., Pike, R. M., and Coggeshall, H. C.: Specificity of Differential Sheep Cell Agglutination Test in Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **70**:475, 1949.
23. Miller, J. E., Lynch, E. R., and Lansbury, J.: Failure of Sensitized Sheep Cell Agglutination to Clarify the Diagnosis of Rheumatic Disease, J. Lab. & Clin. Med. **34**:1216, 1949.
24. Jawetz, E., and Hook, E. V.: Differential Sheep Cell Agglutination Test in Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **70**:650, 1949.
25. Wager, O.: On the Factor Producing Agglutination of Sensitized Red Cells and Its Relation to the Agglutination of Hemolytic Streptococci in Rheumatoid Arthritis Sera, Ann. med. exper. et biol. Fenniae **28** (Suppl. 8): 154, 1950.
26. Scott, F. E. T.: The Differential Sheep-Cell Agglutination Test in Rheumatoid Arthritis, Lancet **1**:352, 1952.
27. Heller, G., Jacobson, A. S., and Kolodny, M. H.: A Modification of the Hemagglutination Test for Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **72**:316, 1949.
28. Ball, J.: Serum Factor in Rheumatoid Arthritis Agglutinating Sensitized Sheep Cells, Lancet **2**:520, 1950.
29. Svartz, N.: Agglutination With Sensitized Sheep Erythrocytes in Rheumatoid Arthritis, Proc. International Congress of Internal Medicine, Acta med. scandinav. **259**:18, 1951.
30. Svartz, N., and Schlossmann, K.: The Hemagglutination Test With Sensitized Sheep Cells in Rheumatoid Arthritis and Some Other Diseases, Acta med. scandinav. **142**:420, 1952.
31. Alexander, R., and de Forest, G. K.: The Sensitized Sheep Cell Agglutination Reaction in Rheumatoid Arthritis, Am. J. Med. **16**:191, 1954.
32. Ball, J.: Sheep Cell Agglutination Test for Rheumatoid Arthritis. A Clinico-Pathological Study, Ann. Rheumat. Dis. **11**:97, 1952.
33. Pike, R. M., Sulkin, S. E., and Coggeshall, H. C.: Persistence of the Factor in Rheumatoid Arthritis Serum Agglutinating Sensitized Sheep Cells, Bact. Proc. 87, 1950.
34. Heller, G., Jacobson, A. S., Kolodny, M. H., and Schuman, R. L.: The Hemagglutination Test for Rheumatoid Arthritis. I. An Immunological Analysis of the Factors Involved in the Reaction, J. Immunol. **69**:27, 1952.

OL.
5
957

35. Jacobson, A. S., Kammerer, W. H., Wolf, J., Epstein, W. V., and Heller, G.: The Hemagglutination Test for Rheumatoid Arthritis. III. Clinical Evaluation of the Sheep Erythrocyte Agglutination (S.E.A.) Test and the Gamma Globulin (F_{II}) Tests, Am. J. Med. **20**:490, 1956.
36. Svartz, N., and Schlossmann, K.: A Serum Cold Precipitable Hemagglutinating Factor in Rheumatoid Arthritis, Acta med. scandinav. **149**:83, 1954.
37. Ziff, M., Brown, P., Lospalluto, J., Badin, J., and McEwen, C.: Agglutination and Inhibition by Serum Globulin in the Sensitized Sheep Cell Agglutination Reaction in Rheumatoid Arthritis, Am. J. Med. **20**:500, 1956.
38. Craig, H. W., Kerby, G. P., and Persons, E. L.: Results of a Modified Rheumatoid Hemagglutination Test: Correlation of Results With Occurrence of C-Reactive Protein, J. Lab. & Clin. Med. **49**:635, 1957.
39. Hess, E. V.: Tests for Rheumatoid Arthritis, Brit. M. J. **1**:1426, 1956.
40. Hobson, D., and Gorill, R. H.: Agglutination Test for Rheumatoid Arthritis, Lancet **1**:389, 1952.
41. Bernstock, L., Bedson, H. S., and Glyn, J. H.: Assessment of a New Hemagglutination Test for Rheumatoid Arthritis, Brit. M. J. **1**:1151, 1956.
42. Erickson, J. O., Volkin, E., Craig, H. W., Cooper, C. R., and Neurath, H.: Biologic False Positive Reactions in Serologic Tests for Syphilis. II. Preparation and Properties of Serologically Active Serum Euglobulin Fractions, Am. J. Syph. **31**:374, 1947.
43. Heller, G., Jacobson, A. S., Kolodny, M. H., and Kammerer, W. H.: The Hemagglutination Test for Rheumatoid Arthritis. II. The Influence of Human Plasma Fraction II (Gamma Globulin) on the Reaction, J. Immunol. **72**:66, 1954.
44. Boyden, S. V.: The Adsorption of Proteins on Erythrocytes Treated With Tannic Acid and Subsequent Hemagglutination by Antiprotein Sera, J. Exper. Med. **93**:107, 1951.
45. Singer, J. M., and Plotz, C. M.: The Latex Fixation Test. I. Application to the Serologic Diagnosis of Rheumatoid Arthritis, Am. J. Med. **21**:888, 1956.
46. Plotz, C. M., and Singer, J. M.: The Latex Fixation Test. II. Results in Rheumatoid Arthritis, Am. J. Med. **21**:893, 1956.
47. Pike, R. M., Sulkin, S. E., Coggeshall, H., and Burdette, R. I.: Serological Reactions in Rheumatoid Arthritis, J. Lab. & Clin. Med. **41**:880, 1953.
48. de Forest, G. K., Mucci, M. B., and Boisvert, P.: The Clinical Behavior of the Hemagglutination Test for Rheumatoid Arthritis, Am. J. Med. **21**:897, 1956.
49. Winblad, S.: Studies on Agglutination of Sensitized Sheep Cells in Rheumatic Diseases. I. Agglutination Titer After Preliminary Absorption of Serum by Sheep Cells, Acta med. scandinav. **142**:450, 1952.
50. Steinbrocker, O., Traeger, C. H., and Batterman, R. C.: Therapeutic Criteria in Rheumatoid Arthritis, J.A.M.A. **140**:659, 1949.
51. Ziff, M., Fallet, G., Carmel, P., DiTata, D., and McEwen, C.: Results of the Sensitized Sheep Cell Agglutination Test in Chronic Arthritic Disease, Presented at the Third Interim Scientific Session, American Rheumatism Association, Nov. 1956, Bethesda, Md.
52. Sharp, J.: Deep X-Ray Therapy in Spondylitis, Brit. M. J. **1**:619, 1954.
53. Blumberg, B., and Ragan, C.: The Natural History of Rheumatoid Spondylitis, Medicine **35**:1, 1956.
54. Ziff, M., and McEwen, C.: Unpublished Data.
55. Ziff, M., Fallet, G., Esserman, P., Lospalluto, J., and McEwen, C.: The Course of Systemic Lupus Erythematosus During Long-Term Maintenance Therapy, Presented at the Annual Meeting, American Rheumatism Association, June, 1956, Chicago.
56. Good, R. A., Rotstein, J., and Mazzitello, W. F.: The Occurrence of Rheumatoid Arthritis and Diffuse Fibrinoid Diseases in Patients With Congenital and Acquired Agammaglobulinemia, Presented at the Third Interim Scientific Session, American Rheumatism Association, Nov. 1956, Bethesda, Md.
57. Foz, A., Batalla, E., and Barceló, P.: The Agglutination of Sensitized Erythrocytes by the Serum From Patients With Rheumatoid Arthritis, Rev. españ. reumat. Number Dedicated to the Second European Congress of Rheumatology), Barcelona, 1951.
58. Pike, R. M., Sulkin, S. E., and Burdette, R. I.: Serological Reactions in Rheumatoid Arthritis. The Agglutination of Sensitized Human Group O Erythrocytes by Rheumatoid Arthritis Serum, Texas Rep. Biol. & Med. **12**:138, 1954.
59. Foz, A., and Batalla, E.: Autoanticuerpos en le Poliartritis Crónica Progresiva. Método Sencillo de Demonstración con Posibles Aplicaciones Diagnósticas, Rev. de diagn. biologico **3**:460, 1954.
60. Waller, M. V., and Vaughan, J. H.: Use of Anti-Rh Sera for Demonstrating Agglutination Activating Factor in Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **92**:198, 1956.
61. Greenbury, C. L.: Elution of the Rheumatoid Arthritis Factor from Red-Cell Agglutinates, Lancet **2**:644, 1956.
62. Foz, A., and Batalla, E.: Autoanticuerpos en le Poliartritis Crónica Progresiva, Rev. españ. reumat. **6**:142, 1955.
63. Lamont-Havers, R. W.: Nature of Serum Factors Causing Agglutination of Sensitized Sheep Cells and Group A Hemolytic Streptococci, Proc. Soc. Exper. Biol. & Med. **88**:35, 1955.

VOL 5 195

64. Wallis, A. D.: Rheumatoid Arthritis. IV. Hemolytic Streptococcus Precipitin Reactions, Am. J. Med. Sc. **213**:87, 1947.
65. Vaughan, J. H.: Behavior of the Rheumatoid Arthritis Agglutinating Factor with Immune Precipitates, J. Immunol. **77**:181, 1956.
66. Dawson, M. H., Olmstead, M., and Jost, E. L.: Agglutination Reactions in Rheumatoid Arthritis. III. Comparison of Agglutinins and Precipitins for Streptococcus Hemolyticus in Rheumatoid Arthritis Sera, J. Immunol. **27**:355, 1934.
67. Chasis, H., and McEwen, C.: Precipitin Reactions between Hemolytic Streptococci of Various Groups and Immune and Rheumatoid Arthritic Sera, J. Immunol. **31**:439, 1936.
68. Williams, R. R., Stone, S. S., Jenkins, J., Evans, R. L., and Bunim, J. J.: Some Characteristics of the Inhibitor System for the Sensitized Sheep Cell Agglutination Reaction, Presented at the Second Interim Scientific Session, American Rheumatism Association, Dec. 1955, Bethesda, Md.
69. Epstein, W., Johnson, A. M., and Ragan, C.: Observations of a Precipitin Reaction between Serum of Patients with Rheumatoid Arthritis and a Preparation (Cohn Fraction II) of Human Gamma Globulin, Proc. Soc. Exper. Biol. & Med. **91**:235, 1956.
70. Epstein, W., Johnson, A. M., and Ragan, C.: A Precipitin Reaction between Human Gamma Globulin and the Serum of Patients Having Rheumatoid Arthritis, Presented at the Annual Meeting, American Rheumatism Association, June, 1956, Chicago.
71. Pallaczek, E.: Personal communication.
72. Kunkel, H.: Personal communication.
73. Pike, E. M., Sulkin, S. E., and Coggeshall, H. C.: Serological Reactions in Rheumatoid Arthritis. II. Concerning the Nature of the Factor in Rheumatoid Arthritis Serum Responsible for Increased Agglutination of Sensitized Sheep Erythrocytes, J. Immunol. **63**:447, 1949.
74. Thulin, K. E.: The Reaction of Streptococcal Agglutination Relative to the RAS Factor in Rheumatoid Arthritis. I. Acta rheumat. scandinav. **1**:22, 1955.
75. Thulin, K.: The Reaction of Streptococcal Agglutination Relative to the RAS Factor in Rheumatoid Arthritis. II. Acta rheumat. scandinav. **1**:31, 1955.
76. Heller, G., Kolodny, M. H., Lepow, I. H., Jacobson, A. S., Rivera, M. E., and Marks, G. H.: The Hemagglutination Test for Rheumatoid Arthritis. IV. Characterization of the Rheumatoid Agglutinating Factors by Analysis of Serum Fractions Prepared by Ethanol Fractionation, J. Immunol. **74**:340, 1955.
77. Deutsch, H. F., Gosting, L. J., Alberty, R. A., and Williams, J. W.: Biophysical Studies of Blood Plasma Proteins. III. Recovery of γ-Globulin from Human Blood Protein Mixtures, J. Biol. Chem. **164**:109, 1946.
78. Wager, O., and Alameri, E.: Studies of Agglutination in Rheumatoid Arthritis. I. Attempts to Purify the Factor Causing Agglutination of Sensitized Erythrocytes, Ann. med. exper. et biol. Fenniae **31**:361, 1953.
79. Robinson, A. R., Stulberg, C. S., and Kuyper, A. C.: Identification of the Substance Active in Sheep Cell Agglutination Test for Rheumatoid Arthritis, Proc. Soc. Exper. Biol. & Med. **85**:4, 1954.
80. Svartz, N., and Schlossmann, K.: Cold Precipitable Hemagglutinating Factor in Serum From Patients With Rheumatoid Arthritis, Ann. Rheumat. Dis. **14**:191, 1955.
81. Peterson, E. A., and Sober, H. A.: Chromatography of Proteins. I. Cellulose Ion Exchange Adsorbents, J.A.C.S. **78**:751, 1956.
82. Sober, H. A., Gutter, F. J., Wyckoff, M., and Peterson, E. A.: Chromatography of Proteins. II. Fractionation of Serum Protein on Anion Exchange Cellulose, J.A.C.S. **78**:756, 1956.
83. Lospalluto, J., and Ziff, M.: Purification of the Accessory Agglutinating Factor of the Serum in Rheumatoid Arthritis, Presented at the Annual Meeting, American Rheumatism Association, June, 1956, Chicago.
84. Smyth, C. J., and Clark, G. M.: The Relationship of the Polysaccharide Content of the Euglobulin Fraction in Rheumatoid Arthritis Serum to the Agglutination of Sensitized Sheep Erythrocytes, Presented at the Second Interim Scientific Session, American Rheumatism Association, Dec. 1955, Bethesda, Md.
85. Svartz, N., and Schlossmann, K.: Substances Agglutinating Sensitized Sheep Erythrocytes Obtained by Fractionation of Blood Serum With Carbon Dioxide, Acta med. scandinav. **145**:216, 1953.
86. Svartz, N.: Agglutination With Sensitized Sheep Erythrocytes in Rheumatoid Arthritis, Acta med. scandinav. (Suppl. 246) p. 240, 1950.
87. Brown, P.: Unpublished Data.
88. Boettiger, L., Lospalluto, J., and Ziff, M.: Unpublished Data.
89. Svartz, N.: Serological Tests in Rheumatoid Arthritis, Lancet **2**:194, 1956.
90. Pike, R. M., Sulkin, S. E., and Coggeshall, H. C.: The Hemagglutination Test for Rheumatoid Arthritis, M. Clin. North America **39**:384, 1955.
91. Grubb, R.: Agglutination of Erythrocytes Coated With "Incomplete" Anti-Rh by Certain Rheumatoid Arthritic Sera and Some Other Sera, Acta path. et microbiol. scandinav. **39**:195, 1956.

OL.
5
957

VASCULAR LESIONS IN RHEUMATOID ARTHRITIS

LEON SOKOLOFF, M.D., AND JOSEPH J. BUNIM, M.D.

BETHESDA, MD.

From the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Department of Health, Education, and Welfare, Bethesda, Md.

(Received for publication Feb. 5, 1957.)

VASCULAR lesions in rheumatoid arthritis have received increasing attention, as is evident from the fact that in the past five years at least 20 papers have been published relating to the occurrence of vasculitis in this disease. These lesions are of considerable importance for several reasons. They may be of significance in the pathogenesis of rheumatoid arthritis. They may constitute a morphologic link that relates rheumatoid arthritis to other collagen diseases, such as rheumatic fever, systemic lupus erythematosus, systemic scleroderma, and polyarteritis nodosa; for vasculitis occurs in each of these diseases. The possibility that angiitis may be activated in patients with rheumatoid arthritis as a result of prolonged steroid administration has constituted, in the mind of the clinician, an additional and quite formidable hazard associated with hormonal therapy.

During an earlier study of striated muscle in rheumatoid arthritis, it was discovered that inflammatory changes were present in small arteries in approximately 10 per cent of biopsy specimens.[48] Furthermore, evidence was presented that vascular lesions played a role in the development of the subcutaneous nodule.[47] In the past 4 years we have observed 10 additional cases of rheumatoid arthritis exhibiting vasculitis, and these are summarized in this report.

CASE 1.—A 52-year-old white man who had had "rheumatism" at the age of 18 and rheumatic heart disease later, developed rheumatoid arthritis at the age of 45. There was a past history of syphilis complicated by optic atrophy. Two years after arthritis developed he was treated with a gold compound for 6 months. Eight months before he came under observation at Bellevue Hospital, he had received cortisone for one month. On admission he was found to have advanced peripheral rheumatoid arthritis, subcutaneous nodules, an enlarged heart with aortic stenosis and insufficiency, blood pressure of 300/0 and congestive heart failure with hepatosplenomegaly and pleural effusion. Laboratory determinations revealed moderate anemia with mild leukocytosis, elevated erythrocyte sedimentation rate (ESR), an inverted serum albumin/globulin (A/G) ratio, and a negative serologic test for syphilis. He died one week after admission to Bellevue Hospital of congestive heart failure complicated by acute ulcerative colitis, peritonitis, and empyema.

Post-mortem Findings (*B. H. 40411*).—Disseminated arteritis was present in one sternoclavicular joint, pectoral muscle, brachial nerve, and a periadrenal arteriole. Focal necrosis of the media of these vessels was accompanied by impregnation with fibrinlike material. Mononuclear cells, lymphocytes, and fibroblasts infiltrated the adventitia, and endothelial cells were swollen. Inflammatory infiltration of the striated muscle was not present. Fibrosis of other small arteries was observed in the muscle, liver, pancreas, kidney, and peritoneum.

Minute foci of necrosis of the synovial membrane of the sternoclavicular joint were present. These lesions were centered about capillaries. Fibrinlike material infiltrated their walls and the immediately adjacent collagenous tissue. In several instances the lumen of the vessels were occluded by this material.

The other principal anatomical diagnoses were: rheumatoid arthritis; lobular pneumonia; empyema, left lower lobe; calcareous aortic stenosis with insufficiency; acute ulcerative colitis; acute generalized peritonitis.

CASE 2.—A 43-year-old Negro woman developed rheumatoid arthritis in 1946 at the age of 34. A few months after onset she was given injections of a gold compound for one year with moderate improvement. A second course of gold in 1952 was ineffective. Cortisone administration was then started and the patient improved moderately but developed hypertension, mild glycosuria, facial rounding, and hirsutism. Cortisone was discontinued but the arthritis became quite severe and a second course was given in 1953. Again this was stopped because the same side effects recurred and, in addition, a psychosis developed. In January, 1955, prednisone therapy was begun. Psychosis and glycosuria did not recur but by the sixth month of therapy the blood pressure rose to 176/120, purpuric spots appeared intracutaneously, and the patient complained of epigastric pain. Examination disclosed subcutaneous nodules, involvement of numerous joints, elevated ESR, a positive sheep cell agglutination test, negative L.E. cell test, and inversion of serum A/G ratio. X-ray of joints revealed osteoporosis, erosion of cartilage, and destruction of subchondral bone. During the sixteenth month of prednisone administration the patient developed severe paresthesias of both hands and feet, bilateral foot and wrist drop, left facial weakness of the central type, and subsequently anesthesia of upper and lower extremities. One week prior to death, a Grade 2 systolic apical murmur appeared, together with pericardial and pleural friction rubs. X-rays of chest revealed infiltrates in both lung fields and pleural effusion. There also appeared multiple, small, discrete, erythematous, nodular, cutaneous lesions. During her last day she complained of severe abdominal pain, appeared to have lost a large amount of blood, and died suddenly.

Post-mortem Findings (*A56-100*).—Necropsy was performed by Dr. Richard Swarm. Characteristic lesions of polyarteritis nodosa, old and recent, were present in synovial pannus of one sternoclavicular joint, striated muscle, nerve, skin, heart, liver, kidney, pancreas, and a small bronchus. In most instances, the landmarks of the wall were obliterated by fibrinlike material. The surrounding structures were infiltrated by large numbers of inflammatory cells, primarily mononuclear. In other vessels, the arteritis had a more chronic character and the vessel walls were fibrotic (Fig. 1,*A*). The terminal episode was related to hemorrhage from an intrahepatic aneurysm. The other anatomic findings included rheumatoid arthritis, focal interstitial myocarditis, and valvulitis (aortic and mitral leaflets).

CASE 3.—A 64-year-old white man was admitted to the Clinical Center with rheumatoid arthritis of 30 years' duration. There was a history of acute coronary occlusion 3 years previously, followed in 6 months by duodenal ulcer that healed with medical treatment. The arthritis was treated with aspirin and later with steroids as indicated in Table I. Examination disclosed advanced, destructive, deforming, active, peripheral rheumatoid arthritis in numerous joints, subcutaneous nodules, enlarged lymph nodes in axilla and groin, enlarged heart and a soft apical systolic murmur, a slightly enlarged liver, and systolic and diastolic hypertension. Laboratory results showed an elevated ESR and a markedly elevated sheep cell agglutination titer (1:8, 192). Seven months after admission the patient died of severe hemorrhage from duodenal ulcer.

Post-mortem Findings (*A56-108*).—Arteritis was present in both sternoclavicular joints, a sciatic nerve, pancreas, right adrenal gland, spermatic cord, and seminal vesicle. In the spermatic cord and nerve, the lesions were of recent origin: the media was partially necrotic and slightly smudged with fibrinlike material; the intima was edematous and the endothelial cells were enlarged. Lymphocytes, mononuclear and plasma cells infiltrated the adventitia and, to a lesser extent, the media (Fig. 1,*B*). In other areas, there was a variable degree of fibrosis of the intima and adventitia. The inflammatory reaction of an extracapsular small artery of the right adrenal gland was largely healed, and the lumen obliterated by fibrous tissue. Small numbers of chronic inflammatory cells persisted in the periarterial scar. A small artery adjacent to a subcutaneous nodule in the region of the right olecranon process was occluded by fibrous tissue and its elastic lamella was destroyed. The nodules consisted of amorphous detritus encapsulated by scar.

VOL.
5
1957

TABLE I. CLINICAL, LABORATORY, AND MORPHOLOGIC DATA ON 10 CASES OF RHEUMATOID ARTHRITIS WITH VASCULITIS

CASE	AGE AND SEX	SCA TEST	L. E. CELL TEST	DURATION OF ARTHRITIS	PRESENCE OF SUBCUT. NODULES	HORMONAL THERAPY			VASCULAR LESION		
						TYPE	APPROX. TOTAL DURATION	TIME INTERVAL BETWEEN LAST DOSE AND DETECTION OF LESION	PATHOLOGIC EXAM.	TYPE	SITE
1*	52 M.	ND	ND	7 yr.	Yes	Cortisone	1 mo.	8 mo.	Necropsy	P.A.N.	Synovial membrane, nerve, muscle, adrenals, kidney, pancreas, liver
2†	43 F.	Pos.	Neg.	10 yr.	Yes	Cortisone Prednisone	14 mo. 18 mo.	None	Necropsy	P.A.N.	Synovial pannus, nerve, skin, liver, kidney, pancreas, coronary arteries, muscle
3	64 M.	Pos.	ND	30 yr.	Yes	Cortisone Prednisone Prednisolone	6 mo. 6 mo. 6 mo.	None	Necropsy	P.A.N.	Synovial membrane, nerve, pancreas, adrenals, spermatic cord, seminal vesicles, brain
4	51 M.	Pos.	Neg.	10 yr.	Yes	Δ^1,9α FF	23 days	3 days	Necropsy	P.A.N.	Testis
5†	65 F.	Pos.	Neg.	7 yr.	Yes	Cortisone Prednisone	6 wk. 18 mo.	None	Necropsy	P.A.N. Subacute arteritis	Sciatic nerve Coronary artery
6	31 F.	ND	Neg.	12 yr.	Yes	Cortisone	2 yr.	9 mo.	Biopsy	P.A.N.	Striated muscle
7	50 M.	Pos.	Neg.	13 mo.	Yes	Cortisone Prednisone Corticotropin Δ^1,9α FF	2 mo. 9 mo. 6 mo. 4 mo.	10 mo. 4 wk. None None	Biopsy	P.A.N. Arteritis	Muscle Early nodule
8	45 M.	Pos.	Neg.	19 mo.	Yes	None	—	—	Biopsy	Arteritis	Early nodule
9*	30 F.	ND	ND	6 mo.	Yes	None	—	—	Biopsy	Arteritis	Early nodule
10	38 F.	Neg.	Neg.	12 mo.	Yes	None	—	—	Biopsy	Angiitis	Synovial membrane

P.A.N. = Segmental inflammation of small arteries which in at least one site had characteristics of polyarteritis nodosa.
SCA = Sheep cell agglutination.
ND = Not done.
Δ^1,9α FF = Δ^1,9α—fluorohydrocortisone.
*These patients had coexisting inactive rheumatic heart disease.
†These patients had rheumatoid heart disease: valvulitis, coronary arteritis, and interstitial myocarditis.

No cellular palisade persisted. There were no vascular lesions or inflammatory infiltration of striated muscle from two different areas.

The remaining principal diagnoses were: rheumatoid arthritis, chronic ulcer of duodenum with massive gastrointestinal hemorrhage; atherosclerosis, generalized, severe; fibrous scar of myocardium.

VOL.
5
1957

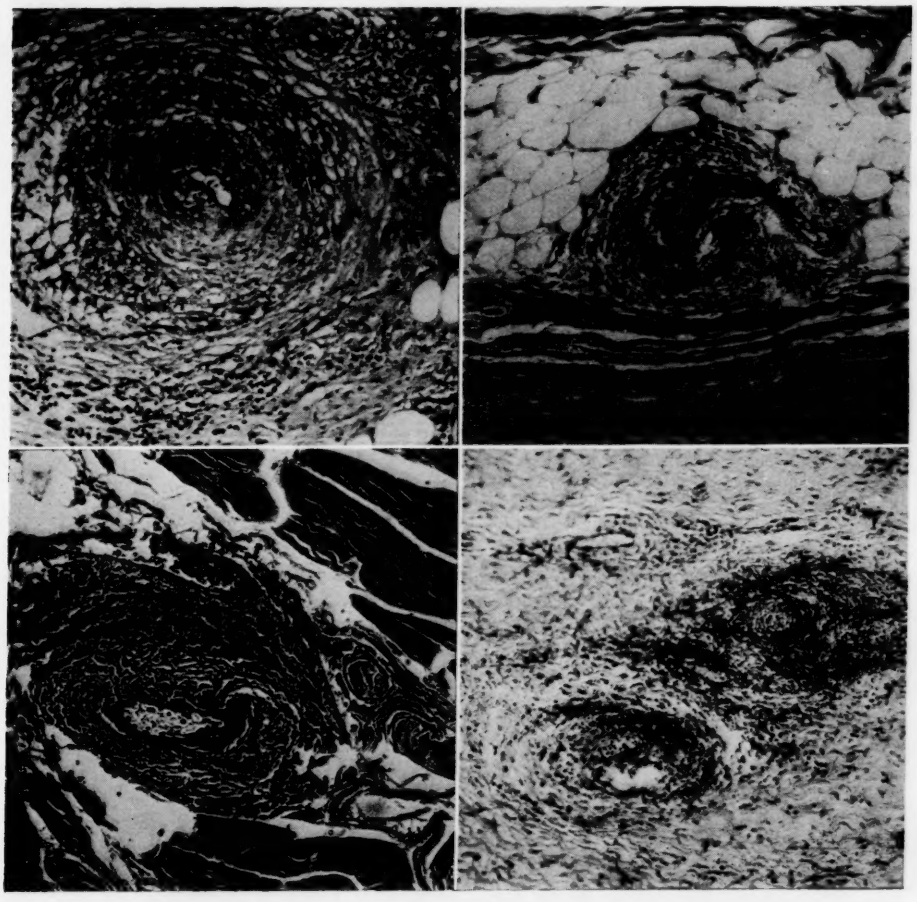

Fig. 1.—Vascular lesions in rheumatoid arthritis. *A*, Case 2. This lesion in subcutaneous tissue is indistinguishable from polyarteritis nodosa. (Hematoxylin and eosin; × 87.) *B*, Case 3. Arteritis in sciatic nerve. (Hematoxylin and eosin; × 87.) *C*, Case 6. Polyarteritis nodosa in striated muscle. (Hematoxylin and eosin; × 80, approximately.) *D*, Case 10. Miliary areas of early necrosis and cellular infiltration in synovial membrane center about minute blood vessels. The smudged appearance of surrounding fibers is due to "fibrinoid" swelling and discoloration with necrotic nuclear material. (Hematoxylin and eosin; × 100.)

CASE 4.—A 51-year-old white man gave a history of rheumatoid arthritis that began 10 years ago and that had been treated at one period with 40 injections of a gold compound. He had never received steroids. On examination he was found to be poorly nourished, and he had typical, advanced, active peripheral rheumatoid arthritis with severe atrophy of the muscles,

subcutaneous nodules, pulmonary emphysema and fibrosis, and an enlarged heart. Laboratory findings consisted of an elevated ESR and leukocytosis, an inverted serum A/G ratio, a positive sheep cell agglutination test and a negative L.E. cell test. During his admission he was given a trial of delta-1, 9 alpha-fluorohydrocortisone for 23 days. He developed acute coronary occlusion and died three days later.

Post-mortem Findings (*A55-133*).—Necropsy was performed by Dr. L. B. Thomas. In two sections of the left testis, active inflammatory reaction was found in four small arteries. In each, there was a prominent infiltrate of inflammatory cells in the adventitia, composed principally of lymphocytes. A smaller proportion of mononuclear cells and fewer polymorphonuclear neutrophils and eosinophils was included. Focal necrosis of the media of variable proportion was present. In one artery, a small proportion of the necrotic media was smudged with fibrinlike material. Proliferation of fibroblasts was seen in the intima and adventitia of one of these vessels. In two other arteries, there was marked thickening of the intima and advantitia by fibrous tissue but no inflammatory exudate was present. The remaining arteries were normal. Patchy atrophy and sclerosis of seminiferous tubules were seen in the vicinity of vascular lesions and elsewhere. No vascular lesions were present in a section of the right testis. The seminiferous tubules were not atrophic in this instance.

Active arteritis was not observed in other locations. A scarred artery, like those described in the testis, was present outside the capsule of one adrenal gland. The sternoclavicular joints were involved in a massive process of granulomatous arthritis like that seen in the subcutaneous nodules of rheumatoid arthritis. In several areas, capillaries in the vicinity of zones of necrosis were occluded by fibrinlike material that enmeshed erythrocytes. The other principal anatomic findings were atherosclerosis and thrombosis of the coronary artery with recent myocardial infarction; fibrous pericardial obliteration; rheumatoid arthritis.

Case 5.—A 65-year-old white women was admitted to the Clinical Center in 1954, bedridden with rheumatoid arthritis which developed in 1949. She had been given cortisone for approxi-

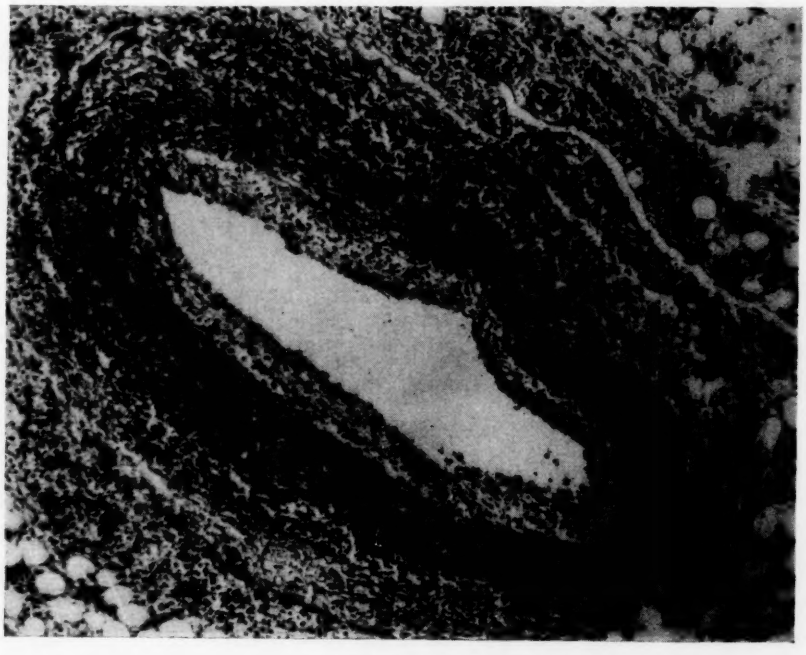

Fig. 2.—Case 5. Subacute coronary arteritis is characterized by infiltration of inflammatory cells into all layers of the wall and the perivascular fibroadipose tissue. There is no necrosis of the media. (Hematoxylin and eosin; × 70.)

mately 3 weeks in 1950 and again in 1951, with marked improvement and no adverse effects. In 1954, examination disclosed advanced, deforming rheumatoid arthritis of numerous joints, subcutaneous nodules, bilateral episcleritis, an enlarged heart with an apical systolic Grade 2 murmur, moderate anemia, markedly elevated ESR, negative L.E. cell test, and sheep cell agglutination titer of 1:2,048. Roentgenograms showed destruction of articular cartilage and subchondral bone and several ankylosed joints. Prednisone therapy instituted Dec. 28, 1954, was followed by marked improvement and the patient became ambulatory with the aid of canes. In July, 1955, she developed a duct cell carcinoma of the breast and a radical mastectomy was done at once. Because of diminishing therapeutic response to prednisone, the steroid was discontinued in April, 1956. In June, 1956, bilateral pneumonia (or possibly pulmonary embolism) with pleural effusion and thrombophlebitis of the right iliac vein supervened. Prednisone therapy (5 mg. daily) was reinstituted on July 7, but the patient failed to respond, developed congestive heart failure and bouts of paroxysmal auricular tachycardia. An electrocardiogram revealed right bundle branch block. The patient died in July, 1956.

Post-mortem Findings (*A56-114*).—Necropsy was performed by Dr. Philip H. Geisler. No metastatic carcinoma was found. The heart was enlarged and weighed 500 grams. The pericardial cavity was obliterated by fibrous adhesions. Several nodular areas of induration and calcification were present in the base and annulus of the mitral and tricuspid valves. Microscopically, a chronic inflammatory reaction was observed in the mitral leaflet. Two geographic areas of hyalinization and necrosis were present within the infiltrated area. Nuclear debris were present within these and they were surrounded by an incomplete palisade of elongated connective tissue cells. Calcific material was present near, but not within, these areas of necrosis. The hyaline valve substance did not have a fibrinlike character with phosphotungstic acid-hematoxylin stain. Numerous interstitial infiltrates of mononuclear cells and fibroblasts with fewer eosinophils and polymorphonuclear leukocytes were present in the myocardium. In the epicardium of the left ventricle, several small coronary artery branches were inflamed. Mononuclear cells and a smaller proportion of fibroblasts, eosinophils, and lymphocytes infiltrated and thickened the intima and adventitia. The media was not necrotic but numbers of inflammatory cells were present within it (Fig. 2). Healed and active necrotizing arteritis were present in the sciatic nerve. These lesions were indistinguishable from polyarteritis nodosa.

CASE 6.—A 31-year-old Negro women was observed in the Arthritis Clinic of Johns Hopkins Hospital for severe, advanced, deforming, peripheral rheumatoid arthritis. She had received cortisone intermittently during the preceding 3 years. Examination disclosed in addition to arthritis, subcutaneous nodules, unilateral proptosis, and motor weakness of the left twelfth, the right seventh, and sensory impairment of the right fifth cranial nerves, a blood pressure of 140/110, an elevated ESR, a negative L.E. cell test, and mild albuminuria. A muscle biopsy had revealed polyarteritis nodosa (see below). Two years later, the patient was readmitted to Johns Hopkins Hospital with retinal detachment and severe hypertension. She died 4 weeks later in congestive heart failure and uremia.

Biopsy of Gastrocnemius Muscle (*S37821*).—In a few of the serial sections of striated muscle, the landmarks of a small artery were found to have been destroyed in large part (Fig. 1,*C*). The intima and media were in large part replaced by material that resembled compact fibrin, while the more external portions consisted of fibrous tissue. Within the lumen was a fine coagulum of retiform fibrin. A compact exudate of chronic inflammatory cells was present in the perivascular tissue.

CASE 7.—A 50-year-old white man with a history of "growing pains," without arthritis or carditis during childhood, was admitted with rheumatoid arthritis of 12 months' duration. He had recurrent attacks of "hay fever" each summer. Intensive and continuous hormonal therapy was instituted soon after onset of his arthritis (Table I). Examination disclosed severe, active rheumatoid arthritis in many joints without deformities or radiographic evidence of destruction of bone or articular cartilage, subcutaneous nodules, and a labile blood pressure which reached a maximum of 168/96. The laboratory findings included an elevated ESR, leukocytosis, inverted serum A/G ratio, positive sheep cell agglutination test, and a negative L.E. cell test. During observation he developed thrombophlebitis of a vein in the left leg complicated by a pulmonary infarct. He received anticoagulant therapy, and was discharged much improved.

VOL.
5
1957

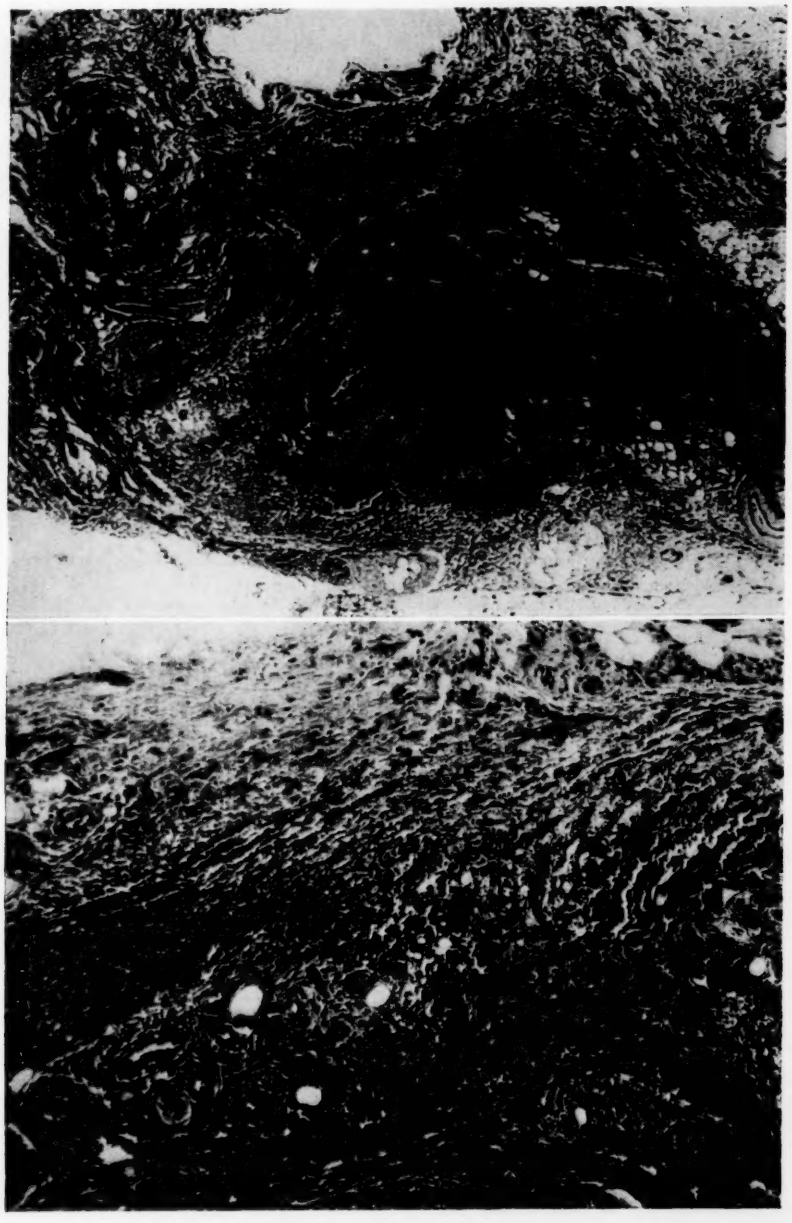

Fig. 3.—Case 7. Early subcutaneous nodule from olecranon region. *A*, A small artery lies in the center of the lesion. The lumen is filled with a fibrinike coagulum. The internal elastic membrane has been destroyed at several points. (Orcein, hematoxylin and eosin; × 27.) *B*, Higher magnification of section cut through peripheral portion of tissue from same block as 3,*A*, showing zone of "fibrinoid" necrosis in the nodule. Although there is no well-developed cellular palisade, the lesion is otherwise quite characteristic of a subcutaneous nodule of rheumatoid arthritis. (Hematoxylin and eosin; × 87.)

While receiving daily corticotropin and weekly gold compound injections, new subcutaneous nodules were appearing. One such nodule, 7 days old, located 9 cm. proximal to styloid process of ulna was biopsied. Two weeks later while same therapy was continued, biopsy of the gastrocnemius muscle was done.

Biopsy of Subcutaneous Nodule (*S56-11*).—The specimen was received in four portions. The greatest dimension of any of these was 0.8 cm. Serial sections revealed a multicentric process of "fibrinoid" necrosis of subcutaneous tissue and formation of compact vascular granulation tissue centering about small arteries (Fig. 3,*A*). Segments of the arteries and some of the newly formed vessels were occluded by a coagulum of fibrinlike material that incorporated erythrocytes, scattered polymorphonuclear leukocytes, and connective tissue cells like those of the surrounding granulation tissue. Much of the granulation and compact collagenous tissue had undergone necrosis. There were geographic areas in which the fibers had variously become swollen and assumed an affinity for phosphotungstic acid-hematoxylin and other fibrin stains or were fragmented (Fig. 3,*B*), and smudged with nuclear debris. At the margin of these zones of necrosis was a cellular border of proliferating, plump connective tissue cells and thick-walled capillaries, but no distinct cellular palisade. There was a scattering of lymphocytes about some of the vessels and numbers of polymorphonuclear leukocytes infiltrated the walls of the arteries in places.

VOL.
5
1957

Fig. 4.—Case 7. Segmental necrotizing arteritis in striated muscle of patient illustrated in the preceding figure. The lesion cannot be distinguished from polyarteritis nodosa. Hematoxylin and eosin; × 87.)

Biopsy of Gastrocnemius Muscle (*S56-94*).—At several levels in serial sections of striated muscle, segments of small arteries were involved in an active or healed inflammatory reaction. In Fig. 4 is illustrated a small artery that has undergone focal necrosis. At a point of bifurcation, the landmarks of the wall have become obliterated by material resembling compact fibrin. Similar material protrudes for a slight distance in to the adventitia of the vessels. Inflammatory cells, predominantly mononuclear, are present at the margins of the necrotic tissue and there is some mild fibrosis of the adjacent intima and adventitia.

CASE 8.—A 45-year-old Negro man was admitted with a history of rheumatoid arthritis of 19 months' duration which was treated conservatively with aspirin. He had received only

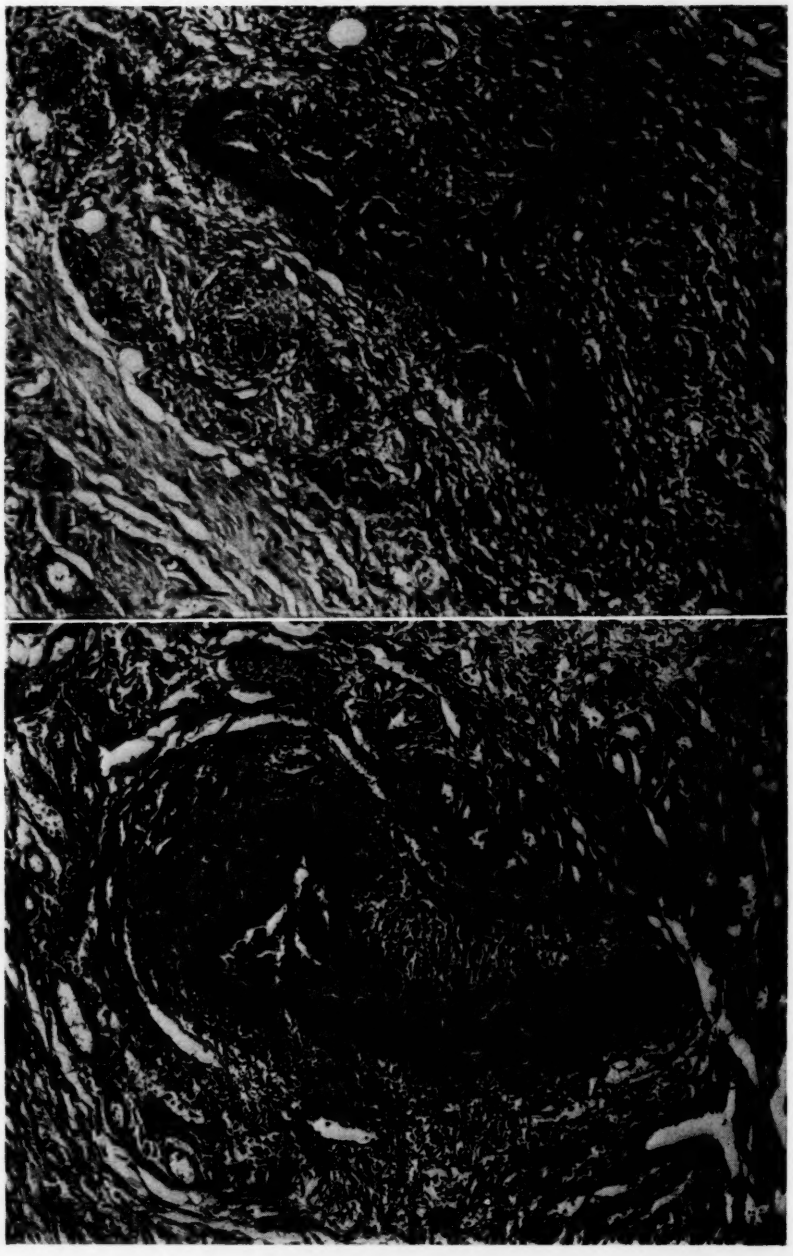

Fig. 5.—Arteritis in early subcutaneous nodule of rheumatoid arthritis. *A*, Case 8. The artery is surrounded by a collar of vascular granulation tissue that penetrates through the central portion of its wall. The internal elastic membrane is disrupted in this region. The lumen is occupied by a coagulum of fibrinlike material and erythrocytes. (Orcein, hematoxylin and eosin; × 87.) *B*, Case 9. A small artery lies within highly vascular granulation tissue. Its wall is disrupted at several points by mononuclear and elongated connective tissue cells that are proliferating radially into the surrounding granulation tissue. The internal elastic membrane has disappeared from much of the wall. A fibrinlike coagulum, that enmeshes neutrophils and monomuclear cells fills the lumen. (Orcein, hematoxylin and eosin; × 80, approximately.)

two intramuscular injections of a gold compound and discontinued chrysotherapy at his own discretion. Prior to biopsy (see below) he had never been given corticotropin or steroid therapy. Past history included gonococcal arthritis and syphilis; the latter had been treated with arsenicals and penicillin. He had lost 30 pounds during the first year of arthritis. Examination disclosed moderately severe and symmetrical rheumatoid arthritis of many joints, subcutaneous nodules, mild axillary, and epitrochlear adenopathy, moderate anemia, elevated ESR, persistently negative L.E. cell test, and a markedly elevated sheep cell agglutination titer (1:112,000). Months after biopsy was done the patient developed acute diffuse interstitial pulmonary fibrosis, pleurisy with effusion, and pericarditis. He recovered and was discharged improved.

Concomitant with a spontaneous flare of arthritis in many joints bilaterally, small, vague subcutaneous nodules appeared at both elbows distal to the olecranon. One of the nodules was biopsied on the ninth day of its appearance.

Biopsy of Subcutaneous Tissue, Region of Right Olecranon Process (S54-52).—The specimen was an elliptical piece of skin and subcutaneous tissue that measured 1.9 × 0.2 cm. externally and was 1.8 cm. deep. One hundred and fifty serial sections were made. They revealed confluent areas of early rheumatoid nodule formation. The lesion was characterized by (1) widespread edema and focal necrosis of the subcutaneous collagenous tissue; (2) nodular proliferation of vascular granulation tissue, at the periphery of which frequently was a palisade of elongated connective tissue cells; (3) inflammatory reaction and occlusion of several arteries and newly formed vessels by material resembling compact fibrin. The artery illustrated in Fig. 5,*A* was located within a nodular area of granulation tissue. Segments of its wall, including the internal elastic membrane, had disappeared and were replaced by granulation tissue continuous with that in the perivascular nodule. The lumen was occupied by a coagulum of fibrinlike material and erythrocytes, into which the connective tissue cells were growing. At another level in the nodule, a small artery within an area of necrosis was itself necrotic and occluded by thrombus material.

Punch Biopsy of Synovial Membrane of the Knee (S54-36).—Sections revealed acute and chronic synovitis but no angiitis.

Biopsy of Gastrocnemius Muscle (S54-38).—No arteritic changes were present.

CASE 9.—A 30-year-old white woman was seen in the Arthritis Clinic of Johns Hopkins Hospital because she had polyarthritis and morning stiffness of 6 months' duration. During the past year the patient noted paresthesias of hands and feet, easy fatigability, and a weight loss of 30 pounds. Her mother had rheumatoid arthritis for 20 years. The patient denied a history of polyarthritis, carditis, or chorea in the past. During both pregnancies she was told by her physician that her heart sounds were "a little strange." Joint pains were relieved "fairly well," but not dramatically, by aspirin. She had never received hormonal therapy. Examination disclosed swollen, tender, warm, red, stiff, and painful proximal interphalangeal joints, wrists, shoulders, and ankles. Subcutaneous nodules were present near both olecranon processes. At the cardiac apex a loud rumbling diastolic and blowing systolic murmur were heard. The electrocardiogram was normal. There was a mild leukocytosis and an elevated ESR. X-rays of the joints showed no definite changes. The diagnosis was active, early peripheral rheumatoid arthritis and well-compensated, inactive rheumatic heart disease with mitral stenosis and insufficiency.

A subcutaneous nodule located 2 inches distal to right olecranon process was biopsied 21 days after it was first observed clinically. The nodule was not present at a clinic visit one month previously.

Biopsy of Subcutaneous Nodule (S37-539).—The specimen was excised in two portions. The greatest dimension of either one was 4 mm. Serial sections of one fragment disclosed a characteristic minute subcutaneous nodule of rheumatoid arthritis. It was surrounded by a zone of moderately compact though vascular granulation tissue. The other fragment of tissue was composed largely of a margin of granulomatous nodule. At one level, immediately external to the nodule, a small artery, approximately 45 μ in external diameter, lay within an island of vascular granulation tissue (Fig. 5,*B*). Large segments of its wall were acutely inflamed and necrotic. Fibrinlike material impregnated the wall in these areas and also occupied the lumen. Erythrocytes and a few polymorphonuclear leukocytes were incorporated in the occluding material. Endothelial and elongated connective tissue cells were proliferating from the marginal portions of the necrotic vessel into surrounding granulation tissue.

VOL.
5
1957

Biopsy of Synovial Membrane of Knee (S37-725).—Sections revealed a florid proliferation of vascular granulation tissue that was infiltrated by mononuclear and plasma cells. No necrotizing vascular lesions were present.

Biopsy of Gastrocnemius Muscle (S37-725).—Serial sections failed to disclose arteritic changes.

CASE 10.—A 38-year-old white woman with rheumatoid arthritis of one year's duration was seen at the Arthritis Clinic of George Washington University Hospital. Numerous subcutaneous nodules appeared, yet the sheep cell agglutination test was negative. The ESR was elevated and the L.E. cell test was negative. She had never received hormonal therapy.

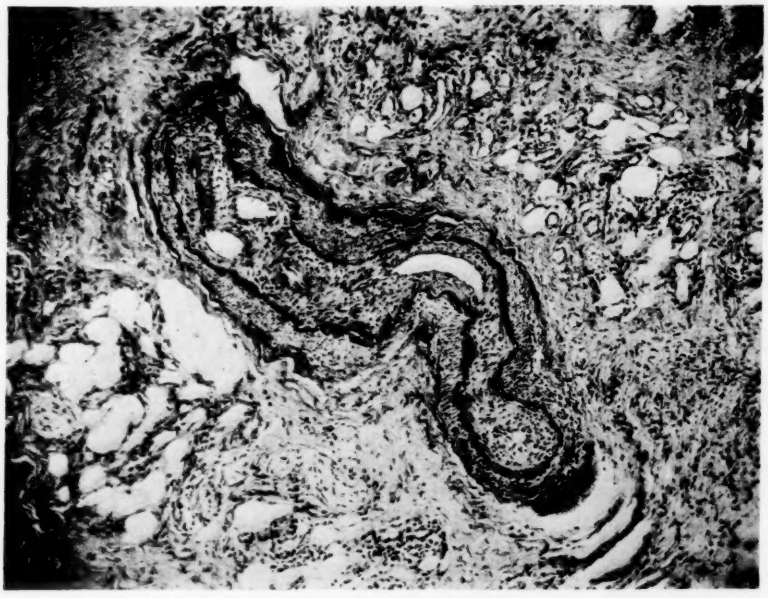

Fig. 6.—Case 10. (Same case as Fig. 1,*D*.) A subcutaneous artery adjacent to the nodule overlying the left ulna is occupied by fibrous tissue and several endothelial-lined channels. At several points the media is involved in the fibrosis that is present in the perivascular fibroadipose tissue. (Orcein, hematoxylin and eosin; × 100.)

Biopsy of Synovial Membrane of Right Elbow (S39630A).—Sections revealed a chronic inflammatory reaction with fibrosis and vascular proliferation in synovial membrane. Much of the surface had undergone "fibrinoid" necrosis and had become fragmented. Focal areas of similar change were seen deeper in the wall. At one point (Fig. 1,*D*), two miliary foci of recent necrosis and inflammation were present. In each instance, a minute blood vessel occupied the center of the lesion. In one, the collagen fibers of the wall and perivascular tissue appeared swollen and eosinophilic. Polymorphonuclear leukocytes and mononuclear cells infiltrated the synovial membrane about the vessels. Some of them were becoming fragmented and the adjacent fibers were smudged with nuclear material. The lumen of the other vessel was apparently occluded by swollen endothelial cells and a coagulum of fibrin and erythrocytes.

Biopsy of Skin Nodule, Left Forearm (S39630B).—The tissue was an irregularly shaped fragment measuring 1.1 × 0.4 × 0.2. Most of it consisted of scar tissue with large areas of "fibrinoid" necrosis like those of a subcutaneous nodule of rheumatoid arthritis. Few cells were present at the margin of the zones of necrosis. In the adjacent subcutaneous adipose tissue, the lumen of a small artery was occupied by cellular fibrous tissue that contained several endothelium-lined channels (Fig. 6). The internal elastic membrane was intact in most places but there were minute areas of splitting and disruption. The adventitia was scarred. Fibrosis extended into the media at several points.

VOL.
5
1957

CLINICAL DATA

As seen in Table I, the 10 patients with rheumatoid arthritis who had vascular lesions varied in age from 30 to 65 years, and the duration of arthritis ranged from 3 months to 30 years. It is impressive that in this series every patient had subcutaneous nodules. The significance of this observation is not clear at this time. In our first reported series of 6 patients with arteritis[47] only 1 had subcutaneous nodules. In the group of 16 patients with rheumatoid arthritis and extensive visceral involvement reported by Sinclair and Cruickshank,[46] 9 had arteritis but only 1 had subcutaneous nodules. In Ball's collection[3] of 5 cases with rheumatoid arthritis and polyarteritis nodosa, subcutaneous nodules appeared in 3. The sheep cell agglutination titers in our series were markedly elevated in 3 cases (Cases 3, 5, and 8), the reaction being positive in serum dilutions of 2,048, 8,092, and 112,000.

Two patients (Cases 1 and 9) had chronic inactive rheumatic heart disease. Two patients (Cases 2 and 5) had rheumatoid heart disease with mitral aortic and tricuspid valvulitis, interstitial myocarditis, and subacute coronary arteritis. One patient had a myocardial infarct from which he had recovered (Case 3) and another died 3 days after coronary thrombosis (Case 4). In both cases, coronary disease was due to atherosclerosis. Two patients experienced thrombophlebitis with pulmonary emboli (Cases 5 and 7).

A prominent feature in 2 of 7 cases (2 and 6) with polyarteritis nodosa was neuropathy of cranial and peripheral nerves associated with motor and sensory changes. Persistent hypertension occurred in 4 cases with polyarteritis nodosa. In only one of these, the blood pressure before the administration of prednisone was known to be normal. By the sixth month of therapy it had risen from 124/76 to 176/120. In the other 6 cases in this series the blood pressure was within normal limits. Splenomegaly, hepatomegaly, and lymphadenopathy were present in several cases. Only one patient (Case 7) had an allergic disease ("hay fever").

All patients had an elevated ESR, only a few had leukocytosis and none leukopenia. Serologic tests for syphilis and L.E. cell tests were negative in all cases. Moderate anemia was present in less than half the cases.

DISCUSSION

Collins[13] stated that vascular lesions do not occur in rheumatoid arthritis except perhaps as a nonspecific component of the intrinsic inflammatory reaction of the affected tissues. Baggenstoss and Rosenberg[1] failed to note lesions in the visceral blood vessels in 30 necropsies of patients with rheumatoid arthritis. The arteritis described by Holsti[26] in rheumatoid arthritis as well as in rheumatic fever is an artifact, in our opinion.

Nevertheless, in a review of the literature on polyarteritis nodosa, Friedberg and Gross,[21] in 1934, found 16 cases associated with rheumatic disease. Some of these cases were regarded as probable infectious or rheumatoid arthritis. Dawson[16] stated that he had seen 3 instances of rheumatoid arthritis in which polyarteritis nodosa was found at necropsy.

That generalized polyarteritis was a frequent finding in rheumatoid arthritis was emphasized by Christie.[11] Ball has cited a personal communication from Ross[3] that he found 8 instances of arthritis indistinguishable from rheumatoid arthritis in 104 histologically proved cases of polyarteritis nodosa. Graef[24] reported two instances of polyarteritis nodosa of coronary vessels in 66 cases of rheumatoid arthritis. Individual instances of polyarteritis nodosa occurring in rheumatoid arthritis have been noted by Zeek[31] and others,[10,12,18,22] in juvenile rheumatoid arthritis by Pirani and Bennett,[41] by Froboese cited by Bini,[8] and in Sjögren's syndrome.[25]

The arteritis observed during our initial study of striated muscle in rheumatoid arthritis did not possess distinctive histologic characteristics, but was believed to be a specific manifestation of the disease because (1) it did not occur in striated muscle in conditions other than rheumatoid arthritis, with the exception of other "collagen diseases"; (2) the process was limited to very small arteries; and (3) the histologic features of the inflammatory reaction were fairly constant: the cells infiltrated the adventitia primarily and the predominant cell type was large mononuclear. The lesions differed from those of polyarteritis nodosa principally in the lack of severe destruction of the wall.

Arteritic lesions were subsequently reported in the heart,[14] nerves,[42] at the margin of a subcutaneous nodule,[38] and infrequently in other viscera.[7,34,39] They were found to occur in the subcutaneous nodule with special frequency during the early phases of its formation.[47] Previously arteritis at the margin of nodules had been reported by Dawson and Boots,[15] and by Keil.[27] Giordano[23] noted that in the period of appearance of subcutaneous nodules, arterial vessels may present fibrinous deposits in the endothelium. Bennett and co-workers[6] had observed the presence of thrombosed blood vessels in young nodules. This finding suggested to the latter observers that injury of blood vessels may sometime be an important factor in the development of the necrosis. Recently isolated instances of vasculitis in the articular tissues early in the course of rheumatoid arthritis have been reported by Kulka and co-workers[33] and by Sinclair and Cruickshank.[46] The intimate association of inflammation of the blood vessels with the early nodule and the coexistence of similar vascular lesions in the striated muscle and synovial membrane of the same patients provided the basis for the concept that angiitis is a feature of rheumatoid arthritis and, moreover, that it plays a role in the development of other lesions associated with this disease. In the rheumatoid granulomata, not only arteries but arterioles and capillaries are affected. Furthermore, in this lesion, unlike that in the striated muscle, occlusion of the lumen by fibrinlike material is seen.

Among the cases in the present report are three instances of early formation of subcutaneous nodules (Cases 7 to 9), in each of which segmental necrosis and occlusion of small subcutaneous arteries has been found. Furthermore, in one of these patients, necrotizing arteritis was demonstrated in the striated muscle by biopsy (Case 7). In another patient (Case 10), early necrosis of the collagenous synovial tissues of the elbow joint was clearly found to center about inflamed capillaries. In the same patient, the lumen of a small artery adjacent to an older subcutaneous nodule was fibrotic and recanalized. Healed or chronic

arteritis was present in the sternoclavicular articular tissues of three patients who had arteritis, morphologically indistinguishable from polyarteritis nodosa, in the striated muscle or peripheral nerve, as well as several viscera.

Consideration has been given to the possibility that vasculitis in rheumatoid arthritis implies a kinship to systemic lupus erythematosus. The relationship of rheumatoid arthritis and systemic lupus erythematosus is uncertain although (1) a sizable proportion of patients with rheumatoid arthritis have positive L.E. cell tests—the figure has been estimated as high as 25 per cent in selected cases[37]; (2) polyarthritis (often chronic and deforming) is a most common manifestation of lupus; (3) visceral lesions, particularly of the heart, are frequently found at necropsy in rheumatoid arthritis; and (4) positive sheep cell agglutination tests occur in a moderately high percentage of patients with lupus erythematosus. In 1950, Bauer commented[9] that he had seen 8 or 10 patients who had rheumatoid arthritis, associated vascular lesions, and positive L.E. cell tests.

VOL.
5
957

It is noted that in all the patients included in the present report the L.E. cell test was negative and other clinical and anatomic characteristics of lupus were absent. We have seen, however, several instances of apparently coexisting lupus and rheumatoid arthritis; in one of these arteritis was present.

The incidence of necrotizing angiitis in rheumatoid patients with induced hyperadrenocorticalism has been viewed with some concern since long term hormonal therapy has been widely used. Although steroid hormones have been employed successfully in suppressing polyarteritis nodosa, in clinical practice as well as in experimental animals, several investigators have noted the development of these lesions following administration of the steroid compounds or corticotropin[7,19,35,44,49,53] to patients with rheumatoid arthritis. Kemper, Baggenstoss, and Slocumb[28] studied the vascular lesions found at necropsy in 54 patients with rheumatoid arthritis. Four of the 14 patients treated with cortisone had disseminated lesions of polyarteritis nodosa whereas none of 38 who had not received cortisone had such lesions. It is noteworthy, however, that in the group of 38 who had not received cortisone, vascular lesions found in 5 patients were considered to be of rheumatic fever origin, and "active acute vasculitis" present in 3 additional cases was thought to be of a "nonspecific" nature. The authors concluded that "in certain susceptible patients with rheumatoid arthritis, the administration of cortisone may precipitate the development of diffuse necrotizing arteritis." Necrotizing vascular lesions with malignant hypertension have also been reported to complicate steroid treatment of scleroderma[2,5] and polyarteritis nodosa.[17]

On the other hand, as has already been pointed out, vascular lesions have been known to antedate these forms of therapy in rheumatoid arthritis. Of the four cases of polyarteritis nodosa complicating rheumatoid arthritis observed by Ball,[3] only one had been treated with cortisone. In 9 cases of acute, subacute, or healed arteritis associated with rheumatoid "disease" reported by Sinclair and Cruickshank,[46] none had received corticotropin or steroids. Cruickshank was of the opinion that the damage to the vessel wall in these lesions was usually less severe than that encountered in polyarteritis nodosa.[14]

In the present series of 10 cases, there are 7 instances of disseminated arteritis in which the patients had been treated for many months with steroids or

corticotropin. In each of these cases there is at least one lesion that is histologically indistinguishable from polyarteritis nodosa, although in many other vessels destruction of the wall is not a conspicuous feature of the arteritis. One patient with Sjögren's syndrome, not included in this series because the joint symptoms were not typical of rheumatoid arthritis, although the sheep cell agglutination test was positive, was found to have, on biopsy of the sartorius muscle, arterial changes typical of polyarteritis nodosa (S55-1559). This patient had never received steroid therapy. In addition, we have had the privilege of examining necropsy tissues from two cases of steroid-treated rheumatoid arthritis studied at other institutions, in which lesions of polyarteritis nodosa were present.

During the three years that followed the opening of the Clinical Center of the National Institutes of Health (July, 1953 to July, 1956), 6 patients with rheumatoid arthritis came to necropsy. Five of the 6 had received steroid therapy before or after admission to the Clinical Center for a period of several months or longer. Four of these 5 patients were found to have disseminated visceral arteritis. Although there are obvious statistical pitfalls in drawing firm conclusions about the role of steroid therapy in potentiating the development of the vascular lesions, there certainly is room for serious concern.

There is experimental information that cortisone may exert a deleterious influence on blood vessels in two circumstances: (1) Thomas[49] has shown that cortisone favors development of the generalized Shwartzman reaction to injection of meningococcal endotoxin in young rabbits; (2) focal ectasia and occlusion of glomerular capillaries develop in rabbits treated with cortisone.[55]

There are a number of questions that arise in relation to the interpretation of the specificity of the vascular lesions as a manifestation of rheumatoid arthritis.

1. *Why aren't the vascular lesions found consistently in rheumatoid arthritis?* The complete answer to this question is not and cannot be forthcoming. Two obvious factors are the stage of development at which the tissues are examined and the extent to which the lesions are sought. In 7 of the 9 early subcutaneous nodules we have studied, conspicuous vascular necrosis and occlusion have been present. Reference has already been made to other studies that have emphasized vascular occlusion in the early stages of nodule formation. It may be presumed that many of the vessels are consumed in the necrosis of the nodule. Furthermore, the angiitis may be manifest at a minute arborization of the vascular tree in the rheumatoid granuloma and have a short lifespan. Even when present, the lesions are frequently scanty and are identified only after numerous sections are made. Careful study of the margins of long-standing nodules will often disclose scarred arteries of the sort illustrated in Fig. 6. It cannot be concluded that these necessarily represent healed primary arteritis rather than a secondary reactive change.

The inconstancy of angiitis in rheumatoid arthritis is likewise found in other collagen diseases. In rheumatic fever, it was found in 21 per cent of cases by Von Glahn and Pappenheimer[50] but in more recent years the reported incidence has been only 5 per cent.[48] In systemic lupus erythematosus, renal arteritis has been found in 40 per cent of one series.[29] The incidence in generalized sclero-

VOL 5 195

derma is less certain, ranging from "few" in the series of Piper and Helwig[40] to "very frequent" in that of Klemperer.[30] It was present in each of 6 cases of systemic scleroderma we have studied, although we recognize this is a selected group.

2. *What is the histological relationship of rheumatiod arteritis to polyarteritis nodosa?* As originally conceived, rheumatoid arteritis was not characterized by an histologic specificity but it was distinguished from polyarteritis nodosa by less conspicuous mural necrosis, less widespread dissemination, and absence of thrombosis.[47,48] It is true, as pointed out by Ball[3] and by others, that side by side with the well-recognized lesions of polyarteritis nodosa, a spectrum of other vascular lesions occurs in arteries, less often in arterioles and venules. It is Ball's view that the variety of arteritic changes found in the rheumatoid patient all fall within the histologic variants of polyarteritis nodosa. He also points out that similar considerations apply to the arteritis of rheumatic fever—that the the arteritis described by Von Glahn and Pappenheimer is a part of the spectrum of polyarteritis nodosa that was found associated with rheumatic fever by Gross and Friedberg and by others. Rich[43] also, regards the arteritis of rheumatic fever as sharing with polyarteritis nodosa a basis in hypersensitivity. Nevertheless, most authorities still classify rheumatic arteritis as a separate category of necrotizing arteritis rather than as polyarteritis nodosa. The reasons for separating rheumatic arteritis from polyarteritis nodosa apply to rheumatoid arteritis as well.

3. *What is the pathologic significance of polyarteritis nodosa in rheumatoid arthritis?* The nosologic status of polyarteritis nodosa has been a subject of much consideration. Three general categories of interpretation have been entertained: (1) polyarteritis nodosa is a *disease* in which a characteristic segmental necrosis and inflammation of arteries occurs; (2) polyarteritis nodosa is a histologic type of segmental necrotizing arteritis that in all instances is a manifestation of hypersensitivity; and (3) polyarteritis nodosa is a histologic type of necrotizing arteritis that may arise from diverse origins. Most pathologists accept the existence of an allergic origin to certain instances of polyarteritis nodosa and Rich has produced lesions of this sort by anaphylaxis in rabbits.[43] Zeek has distinguished, on histologic grounds, between true polyarteritis nodosa and hypersensitivity angiitis.[31] The occurrence of granulomatous lesions in association with arteritis occurs at times under a circumstance in which hypersensitivity has been implicated in the etiology.

Nevertheless, there also occurs a variety of instances of clinical and experimental arteritis, morphologically indistinguishable from polyarteritis nodosa, in which no etiology in hypersensitivity has been established and in which other etiologic factors may well be operating. Outstanding among these is hypertension, as has been noted in man by Wilens and Glynn,[54] Knowles, Zeek, and Blankenhorn,[31] and Bank.[4] In rats, renal infarction has been found by Koletsky[32] to induce polyarteritis nodosa independently of hypertension. Pulmonary arteritis, having many of the morphologic features of polyarteritis nodosa, has been produced in guinea pigs by intravenous introduction of cotton, foreign body emboli.[51] These and many other clinical and experimental bases[52] for a

polyarteritis nodosa type of tissue reaction are recorded. For this reason, we believe it reasonable to regard the polyarteritis nodosa observed in the patient with rheumatoid arthritis as an exaggerated form of rheumatoid arteritis, i.e., arteritis as a specific manifestation of rheumatoid arthritis. There is no evidence at the present time for concluding that the arterial and articular manifestations of rheumatoid arthritis are etiologically related to hypersensitivity.

4. *What relationship do the perivascular infiltrates of lymphocytes in the striated muscle and other structures in rheumatoid arthritis bear to rheumatoid arteritis?* In 1945, Freund, Steiner, and associates[20] described a distinctive lesion of striated muscle in rheumatoid arthritis. It was characterized by focal compact infiltration of lymphocytes and small numbers of other chronic inflammatory cells in and about the muscle fibers. The infiltrate closely resembled the "lymphorrhage" seen in the striated muscle in myasthenia gravis with the exception noted by Russell,[45] that in rheumatoid arthritis the cells are closely related to minute vessels, capillaries, and sometimes arterioles and venules. Because of the minute caliber of these vessels, it is difficult to distinguish between perivascular and intrinsic, albeit adventitial, angiitis. Many pathologists accept such lesions as true angiitis.[36] Such infiltrates are conspicuous in the synovial membrane in rheumatoid arthritis and the young subcutaneous nodule. There are rare instances in which serial sections of such lesions lead to areas of unquestionable mural necrosis or inflammation of vessels of somewhat greater thickness. Nevertheless, as Kulka and co-workers point out,[33] such changes occur in almost any chronic inflammatory process but their pathogenesis and significance are not known. It may be stated, however, that in rheumatoid arthritis, there is no frequent association between the occurrence of these infiltrates in striated muscle and arteritis or polyarteritis nodosa.

SUMMARY AND CONCLUSIONS

The occurrence of inflammatory vascular lesions in rheumatoid arthritis is becoming more commonly recognized. The lesions present a wide spectrum of changes, varying in their histologic character, location, and frequency in different patients. In a proportion of cases, they cannot be distinguished from polyarteritis nodosa. The increasing frequency with which the changes are seen currently, offers cause for concern that in many instances they may possibly result from the deleterious effect of steroid therapy. Nevertheless, such changes unquestionably have occurred in patients who had never been treated with these compounds and there is, at present, no substantial basis to estimate the magnitude of the postulated increased risk of their occurrence as a result of such therapy. As in many other circumstances, the enhanced interest in the subject must increase the frequency and diligence with which the lesions are sought, found, and reported.

Evidence has been presented that inflammatory changes in the arteries are a conspicuous feature of the development of the early subcutaneous nodules of rheumatoid arthritis, and that these are at times associated with arteritis in the striated muscle, synovial tissue, and elsewhere in the same patient. These considerations suggest that the vascular inflammation is an integral feature of rheu-

matoid arthritis. Thus, polyarteritis nodosa in rheumatoid arthritis may be interpreted as an exaggerated form of rheumatoid arteritis rather than as an independent or incidental finding.

Although the observations provide an additional feature of similarity to the several that are already known to exist among the so-called "collagen" diseases, they cannot necessarily be interpreted as proof that these disorders share a common etiology or pathogenesis, or that hypersensitivity is an important mechanism in their development. Thus, in scleroderma, arteritis frequently is associated with development of malignant hypertension and factors related to the hypertension may be critical in the pathogenesis of arterial lesions. In other circumstances, necrotizing angiitis is clearly related to hypersensitivity.

Until more definitive methods for determining the pathogenetic significance of the vascular lesions are available, it would seem to us desirable to retain the concept of a *rheumatoid arteritis*, that is, arteritis as a specific manifestation of the disease and one that contributes, at least occasionally, to the development of the granulomatous lesions that characterize rheumatoid arthritis.

OL.
5
957

ADDENDUM

After this series of cases was collected, two additional patients with rheumatoid arthritis died. One patient had been treated with steroids, but cryptococcosis supervened. Necrotizing arteritis was present in the pancreas and peripheral nerve (A56-158). The second patient, also treated with steroids, had necrotizing arteritis only in peripheral nerves (A57-33).

We wish to acknowledge with gratitude the referral of Cases 6 and 9 by Dr. Charles W. Wainwright, Arthritis Clinic, Johns Hopkins Hospital; Case 10 by Dr. William R. Felts, Jr., Arthritis Clinic, George Washington University Hospital; and permission to include Case 1 by Dr. Marvin Kuschner, Bellevue Hospital.

REFERENCES

1. Baggenstoss, A. H., and Rosenberg, E. F.: Visceral Lesions Associated With Chronic Infectious (Rheumatoid) Arthritis, Arch. Path. **35**:503, 1943.
2. Bagnall, A. W., and Robinson, H. S.: The Development of Fatal "Malignant" Hypertension in a Case of Diffuse Systemic Sclerosis (Scleroderma) in the Course of Treatment With Adrenocorticotropin, (Abstr.) Clin. Res. Proc. **2**:145, 1954.
3. Ball, J.: Rheumatoid Arthritis and Polyarteritis Nodosa, Ann. Rheumat. Dis. **13**:277, 1954.
4. Bank, N.: The Relation of Malignant Hypertension of Periarteritis Nodosa in Humans, J. Mt. Sinai Hosp. **22**:290, 1955.
5. Bartels, E. D., Christensen, L. K., and Ohlsen, A. S.: Renal Affection Complicating Scleroderma, Acta path. microbiol. scandinav. (Suppl.) **105**:174, 1955.
6. Bennett, G. A., Zeller, J. W., and Bauer, W.: Subcutaneous Nodules of Rheumatoid Arthritis and Rheumatic Fever. A Pathologic Study, Arch. Path. **30**:70, 1940.
7. Bevans, M., Nadell, J., DeMartini, F., and Ragan, C.: The Systemic Lesions of Malignant Rheumatoid Arthritis, Am. J. Med. **16**:197, 1954.
8. Bini, G. (cited by): Sulla eziologia reumatica della periarterite nodosa, Gior. clin. med. **33**:687, 1952.
9. Case Records of the Massachusetts General Hospital (Case 36511), New England J. Med. **243**:1003, 1950.
10. Case Records of the Massachusetts General Hospital (Case 37301), New England J. Med. **245**:147, 1951.
11. Christie, G. S.: The General Changes in Rheumatoid Arthritis, in Studies in Pathology Presented to Peter MacCallum, edited by E. S. J. King, T. E. Lowe, and L. B. Cox, Jubilee, Victoria, 1950, Melbourne University Press.
12. Clinico-pathologic Conference (Washington University School of Medicine), Arthritis, Polymyositis and Polyneuritis, Am. J. Med. **20**:462, 1956.

13. Collins, D. H.: The Pathology of Articular and Spinal Diseases, London, 1949, E. Arnold & Company, p. 209.
14. Cruickshank, B.: The Arteritis of Rheumatoid Arthritis, Ann. Rheumat. Dis. **13**:136, 1954.
15. Dawson, M. H., and Boots, R. H.: Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis, J.A.M.A. **95**:1894, 1930.
16. Dawson, M. H., in P. H. Hench and others: The Problem of Rheumatism and Arthritis. Review of American and English Literature for 1938, Ann. Int. Med. **13**:1655, 1940.
17. Ehrenreich, T., and Olmstead, E. V.: Malignant Hypertension Following the Administration of Cortisone in Periarteritis Nodosa, A.M.A. Arch. Path. **52**:145, 1951.
18. Ellman, P., and Ball, R. E.: "Rheumatoid Disease" with Joint and Pulmonary Manifestations, Brit. M. J. **2**:816, 1948.
19. Finck, P. A.: Cortisone Overdosage in Rheumatoid Arthritis, A.M.A. Arch. Path. **60**:374, 1955.
20. Freund, H. A., Steiner, G., Leichtentritt, B., and Price, A. E.: Nodular Polymyositis in Rheumatoid Arthritis, Science **101**:202, 1945.
21. Friedberg, C. K., and Gross, L.: Periarteritis Nodosa (Necrotizing Arteritis) Associated With Rheumatic Heart Disease, With a Note on Abdominal Rheumatism, Arch. Int. Med. **54**:170, 1934.
22. Gaté, J., Coudert, J., and Vayre, J.: Périartérite noueuse ulcérée actuellement guéri par la nivaquine avec sédation complète sous l'effet de se traitement de toutes les manifestations douloureuses d'un très important rhumatisme déformant, Bull Soc. franç. dermat et syph. **2**:174, 1955.
23. Giordano, C.: La polyarthrite chronique primitive. Anatomie pathologique, Omnia méd. **17**:1, 1939.
24. Graef, I., Hickey, D. V., Altmann, V., and Rosenthal, J.: Cardiac Lesions in Rheumatoid Arthritis, Proc. New York Path. Soc. Feb. 26, 1948.
25. Haas, E.: Über die rheumatische Genese einer generalisierten Gefässerkrankung mit Sjögrenschen Syndrom (Dacrio-sialo-adenopathia atrophicans), Arch. path. Anat. **320**:264, 1951.
26. Holsti, Ö.: Beiträge zur Kenntnis der Tonsillen bei den rheumatischen Gelenkaffektionen (akuten, rezidivierenden und chronischen). Eine pathologisch-anatomische und Klinische Studie. Arbeit. a. d., Path. Instr. Univ. Helsingfors. **3**:413, 1923-24.
27. Keil, H.: The Rheumatic Subcutaneous Nodules and Simulating Lesions, Medicine **17**:261, 1938.
28. Kemper, J. W., Baggenstoss, A. H., and Slocumb, C. H.: The Relationship of Therapy With Cortisone to the Incidence of Vascular Lesions in Rheumatoid Arthritis, Ann. Int. Med. (In press.)
29. Klemperer, P.: The Pathogenesis of Lupus Erythematosus and Allied Conditions, Ann. Int. Med. **28**:1, 1948.
30. Klemperer, P.: The Significance of the Intermediate Substances of the Connective Tissue in Human Disease, Harvey Lect. **49**:100, 1953-1954.
31. Knowles, H. C., Jr., Zeek, P. M., and Blankenhorn, M. A.: Studies on Necrotizing Angiitis. IV. Periarteritis Nodosa and Hypersensitivity Angiitis, A.M.A. Arch. Int. Med. **92**:789, 1953.
32. Koletsky, S.: Necrotizing Vascular Disease in the Rat. I. Observations on Pathogenesis, A.M.A. Arch. Path. **59**:312, 1955.
33. Kulka, J. P., Bocking, D., Ropes, M. W., and Bauer, W.: Early Joint Lesions of Rheumatoid Arthritis. Report of Eight Cases, With Knee Biopsies of Lesions of Less Than One Year's Duration, A.M.A. Arch. Path. **59**:129, 1955.
34. Kwasmesky, S., Raszeja, B., and Jasinsky, K.: Zmiany miesniowonaczyniowe w gosccu pierwotnie przewleklym, Polskie Arch. med. Wewn. **24**:157, 1954.
35. Levin, M. H., Rivo, J. B., Scott, W., Figueroa, W. G., Fred, L., and Barrett, T. F.: The Prolonged Treatment of Rheumatoid Arthritis With Cortisone and Corticotropin, Am. J. Med. **14**:265, 1953.
36. McCombs, R. P., Patterson, J. F., and MacMahon, H. E.: Syndromes Associated With "Allergic" Vasculitis, New England J. Med. **255**:251, 1956.
37. McCoy, F. W., Patterson, M., and Freyberg, R. H.: A Study of Disseminated Lupus Erythematosus Diagnosed in Patients Formerly Considered to Have Rheumatoid Arthritis, Ann. Rheumat. Dis. **14**:415, 1955.
38. Nyström, G.: Associated Rheumatoid Arthritis, Periarteritis Nodosa and Felty's Syndrome, Ann. med. int. Fenniae. **42**:52, 1953.
39. O'Brien, D. J., and Storey, G.: Death from Hypersensitivity to Phenylbutazone, Brit. M. J. **1**:792, 1954.
40. Piper, W. N., and Helwig, E. B.: Progressive Systemic Sclerosis. Visceral Manifestations in Generalized Scleroderma, A.M.A. Arch. Dermat. **72**:535, 1955.
41. Pirani, C. L., and Bennett, G. A.: Rheumatoid Arthritis. A Report of Three Cases Progressing From Childhood and Emphasizing Certain Systemic Manifestations, Bull. Hosp. Joint Dis. **12**:335, 1951.
42. Radnai, B.: Vascular Changes in Peripheral Nerves and Skeletal Muscles in Rheumatoid Arthritis, Acta morphol. **3**:87, 1953.

43. Rich, A. R.: Hypersensitivity in Disease With Especial Reference to Periarteritis Nodosa, Rheumatic Fever, Disseminated Lupus Erythematosus and Rheumatoid Arthritis, Harvey Lect. **42**:106, 1946-1947.
44. Robinson, W. D., French, A. J., and Duff, I. F.: Polyarteritis in Rheumatoid Arthritis, Ann. Rheumat. Dis. **12**:323, 1953.
45. Russell, D. S.: Histological Changes in the Striped Muscles in Myasthenia Gravis, J. Path. Bact. **65**:279, 1953.
46. Sinclair, R. J. G., and Cruickshank, B.: A Clinical and Pathological Study of Sixteen Cases of Rheumatoid Arthritis With Extensive Visceral Involvement ('Rheumatoid Disease'), Quart. J. Med. **25**:313, 1956.
47. Sokoloff, L., McCluskey, R. T., and Bunim, J. J.: Vascularity of the Early Subcutaneous Nodule in Rheumatoid Arthritis, A.M.A. Arch. Path. **55**:475, 1953.
48. Sokoloff, L., Wilens, S. L., and Bunim, J. J.: Arteritis of Striated Muscle in Rheumatoid Arthritis, Am. J. Path. **27**:157, 1951.
49. Thomas, L.: Cortisone, ACTH and Infection, Bull. New York Acad. Med. **31**:485, 1955.
50. Von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, Am. J. Path. **2**:235, 1926.
51. Von Glahn, W. C., Hall, J. W., and Sun, S. C.: Arteritis in Guinea Pigs, Produced by Emboli of Cotton, Resembling the Arteritis of Hypersensitivity, Am. J. Path. **30**:1129, 1954.
52. Waters, L. L., and de Suto-Najy, G. I.: Circulatory Factors in the Pathogenesis of Experimental Arteriolar Necrosis, Yale J. Biol. Med. **22**:751, 1950.
53. West, H. F., and Newns, G. R.: Cortisone and Rheumatoid Diseases, Lancet **2**:1123, 1953.
54. Wilens, S. L., and Glynn, J.: Hypertensive and Non-hypertensive Periarteritis Nodosa, A.M.A. Arch. Int. Med. **88**:51, 1951.
55. Wilens, S. L., and Stumpf, H. H.: Nodular and Fatty Glomerular Lesions in Rabbits on Cortisone, Am. J. Path. **31**:275, 1955.

VOL.
5
1957

THE RELATIONSHIP OF RHEUMATOID ARTHRITIS TO PERIARTERITIS NODOSA AND SYSTEMIC LUPUS ERYTHEMATOSUS

CHARLES RAGAN, M.D.

NEW YORK, N. Y.

From the Department of Medicine, Columbia University College of Physicians and Surgeons, and the Edward Daniels Faulkner Arthritis Clinic of the Presbyterian Hospital, New York

(Received for publication Feb. 5, 1957.)

IN RECENT years, certain clinical similarities have been noted between systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and the group of syndromes associated with various types of arterial inflammation.[29] This has led to the speculation that these clinical similarities may denote a closer fundamental relationship, particularly with regard to their pathogenesis. The clinical picture of each of these syndromes is extremely varied, and in only one, SLE, is a specific diagnostic test available.*

To begin with SLE, which may be defined more specifically than the others, little is known of its pathogenesis other than the suspected role of hydralazine[2] as a primary causal agent in certain patients, and sunlight as a provocative agent in other patients.

The syndromes associated with inflammation of blood vessel walls or angiitis are extremely varied. Efforts to single out groups having clinical and possibly prognostic similarities[3] hardly seem worth while when there is such a wide variation in these features. Also the morphologic features reported have changed. Typical periarteritis nodosa with nodular excresences on arterial walls and massive eosinophilia has been reported less frequently in recent times. This may reflect the frequency with which, in the current literature,[4] the usual case report describes extensive involvement of blood vessel walls with a nonspecific inflammatory process which may include necrosis of the wall or only a perivascular cuffing of inflammatory cells. Additional clinical pathologic correlations have been observed. Muscle biopsies showing angiitis have been described in patients with severe penicillin reactions and in severe rhus dermatitis. We have seen hematuria during a penicillin reaction that is probably a reflection of this process in the glomeruli. An element of angiitis may also exist in similar milder reactions due to hypersensitivity. If this viewpoint is carried to its logical conclusion, one will realize that only patients with severe disease are actually labeled with the diagnosis of angiitis and that many others recover without

*This point remains at issue since there are numerous reports suggesting the nonspecificity of the L. E. test. However, when the technique is rigidly standardized, the number of false positives is relatively small[1] and more and more evidence has appeared to verify its specificity, although its sensitivity may be limited.

benefit of an appropriate label. With the known inadequacy of the random muscle biopsy, it is even more apparent that a definite diagnosis of angiitis frequently can be made only in the patient with a fatal outcome where adequate histologic investigation can be carried out. In this syndrome, the patients who die are those in whom the arterial inflammation and subsequent interference with blood supply happens to localize in a vital area. Numerous instances of healed inflammatory lesions have been documented. Thus, if the lesion heals, and, in the process, does not infarct a vital area, the patient will recover and no clue to the basis of the illness will be available. Therefore, when we discuss angiitis, we probably include only a small portion of the total group with the disease. The selection definitely favors a high incidence of patients with fatal disease. In this period of change and confusion, it would seem more reasonable to lump these syndromes together as arterial inflammation or angiitis rather than to attempt, in complete ignorance, to classify them into small, probably specious groupings.[4]

VOL.
5
1957

With regard to pathogenesis, animal experiments have shown that an inflammatory arterial lesion can be produced by the injection of heterologous serum[5] or a component of it.[6] These substances are believed to serve as antigens. The reaction leading to the formation of these lesions appears to be self-limited. In the patient with angiitis, an antigen is frequently not detected and the disease may be self-perpetuating. In order to explain the discrepancies between the patient with angiitis and the animal disease, the phenomenon of autosensitization has been postulated. This postulate remains unproved but is our best guess to date.

In the last of the three clinical syndromes under discussion, rheumatoid arthritis, there is also disagreement as to criteria for diagnosis (particularly in the patient with early disease), poor prognostic yardsticks, and an abysmal ignorance of pathogenesis. Efforts are being made by a Committee of the American Rheumatism Association to elucidate the problem of diagnostic criteria, but it will probably take years of careful, arduous study to place the clinical diagnosis of early rheumatoid arthritis on a firm foundation. The serologic tests for rheumatoid arthritis, when positive, have been found to be fairly specific diagnostic indicators. They may, however, be positive in the serum of patients with SLE and angiitis, so are of limited aid in distinguishing these three disease patterns. Even in late disease, one cannot be certain one is dealing with rheumatoid arthritis alone since the advent of the L.E. preparation. For example, a patient in our clinic with typical rheumatoid arthritis for 10 years and positive serologic reactions, has developed a hemolytic anemia and a positive L.E. preparation. When this occurred, the question was raised whether she had SLE for 10 years or had just recently developed it. An answer is difficult to arrive at in view of two features. First, Moore[7] has shown that the L.E. preparation may become positive only in the latter stages of the disease after a long asymptomatic period in which the only abnormality was a biologic false positive serologic test for syphilis. Second, since the patient has had rheumatoid arthritis by all criteria available to us, one must still consider that this has existed for 10 years even though SLE has apparently supervened.

Prognosis of the patient with rheumatoid arthritis is difficult in all but the most advanced and severe instances of the disease. Even at this level of great severity, we have been surprised by a sudden and totally unforeseen partial remission. In early disease, particularly in mild, early disease, these difficulties in prognosis have made therapeutic evaluation hazardous and have helped to fill the field with its many charlatans. Short and Bauer[8] have developed certain clinical prognostic indices and we[9] have used one of the older serologic reactions, the agglutination of group A hemolytic streptococci, as a prognostic guide, but in all these efforts there are many exceptions and prognosis is on a statistical basis which can scarcely be applied to the individual patient.

When discussing the pathogenesis of rheumatoid arthritis, to say other than that it is unknown, places one in the soothsayer class since nothing really is known about the factors which make an individual with this disease remit, exacerbate, or develop it in the first place.

We are, therefore, discussing the relationship of three clinical syndromes, each of which has an extremely varied clinical picture, great difficulties in diagnosis and prognosis, and only working hypotheses to offer in relation to pathogenesis. It is possible, therefore, that the relationship may be close or there may be none at all. The discussion must be conducted at the clinical level, using the time honored but possibly inaccurate tools of the history, the physical findings, and morphologic pathology. Until we can deal with dynamic mechanisms which have some specificity, we cannot speak with assurance about these diseases individually and certainly not about their relationships to each other.

In a discussion of the relationship of a group of syndromes, the similarities and distinguishing features must be considered. This will be done at three levels—morphologic, i.e., histologic; clinical; and serologic.

MORPHOLOGIC (HISTOLOGIC) CONSIDERATIONS

There seems little difference of opinion that at least *a* primary lesion in both angiitis and SLE is of vascular origin,[10] and there is growing weight of evidence that one primary lesion in rheumatoid arthritis also involves blood vessels, particularly in the genesis of the nodule.[11] It might be stated as an oversimplified generalization that the vascular lesion in angiitis is manifested primarily by inflammation (particularly the cellular components), that in SLE, by necrosis with the peculiar fibrinoid response, and in rheumatoid arthritis by an overgrowth of blood vessel elements as in Sokoloff's[11] concept of the formation of the nodule. In each picture there may be elements of all three processes intermingling but the general pattern holds true for the initial lesion. In some of the more exotic variants such as Wegener's syndrome[12] and malignant rheumatoid arthritis,[13] all three elements appear in the most florid forms.

The distribution of the vascular lesions in each syndrome is, of course, intimately correlated with the clinical picture. In angiitis, the lesion may appear in any blood vessel in the body but our clinical attention is frequently not directed toward it until some vital area—the kidney, brain, or myocardium—is affected. There is no special predilection for involvement of one particular blood vessel. Various eponyms have been attached to syndromes where the

major involvement lies in one particular organ system, e.g., Loeffler's for the lungs, and Wegener's when the upper respiratory tract and kidneys are affected. These particular localizations cannot in the present state of our ignorance be used to invoke a specific pathogenesis.

In SLE, the sites stated to be most commonly involved are the kidneys, spleen, and brain.[14] This again may reflect the interest of the clinician and the pathologist in these vital areas which give warning signs when the patient is alive and are surveyed with particular care at autopsy. When other areas such as muscle, synovial lining, pleura, pericardium, and skin are carefully searched, lesions are not infrequently found. There is one distinguishing feature of SLE which is considered by many to be specific, namely, the hematoxylin body. This is probably composed of the same material present in the L.E. cell and is commonly found in lymph nodes and other nuclear tissues. The composition of this material is now a matter of histochemical debate. Originally, it was thought to be depolymerized desoxyribonucleic acid.[15] Recent evidence would indicate it represents nuclear material from which the histone has been removed.[16]

The lesion which is most typical of rheumatoid arthritis is the rheumatoid nodule. When apparent clinically, it appears over pressure points such as the juxta-articular region of the olecranon, the spine of the scapula, and the occiput. Its morphologic appearance is well known. Its genesis has been a matter of dispute but in recent years Sokoloff's concept[11] that it originates from highly vascular granulation tissue has gained general acceptance. Small vascular lesions actually indistinguishable from a mild form of angiitis may be found[17] in carefully searched random muscle biopsies of patients with obvious rheumatoid arthritis. In what has been termed malignant rheumatoid arthritis,[13] nodular lesions may be found throughout the body in various viscera. The genesis of the nodule may be demonstrated in these patients quite logically, according to the hypothesis set forth by Sokoloff. These patients certainly represent a morphologic link between angiitis and rheumatoid arthritis although, from the viewpoint of history, physical examination, and serologic reactions, they represent severe, far-advanced rheumatoid arthritis with intense and sustained activity. Various opinions have been expressed in an attempt to designate this type of syndrome: malignant rheumatoid arthritis,[13] polyarteritis in rheumatoid arthritis,[18] the arteritis of rheumatoid arthritis,[19] and visceral lesions in rheumatoid arthritis.[30] (Table I.)

CLINICAL CONSIDERATIONS

The clinical pictures of SLE[14] and of rheumatoid arthritis[8,21] have been described more than adequately in numerous monographs. Clinical descriptions of a large group of patients with angiitis are rare as the disease has widely varied manifestations making an "average patient" pattern difficult. No attempt, therefore, will be made to describe the three diseases in clinical detail but their similarities and differences will be discussed.

In recent years, the chronic nature of SLE has become apparent from the work of Moore and his associates[7] in the study of false-positive serologic tests for syphilis. With the widespread use of the L.E. preparation as a bellwether,

VOL.
5
1957

the existence of this disease has often been determined at a time when the clinical picture would be insufficiently defined to reach a diagnosis. The element of chronicity is not usually present in angiitis and the current impression is that in most instances angiitis represents a disease of relatively short duration. Because a definite diagnosis is often made only when the vascular lesions involve vital areas, both SLE and angiitis frequently end fatally. The joint lesion in rheumatoid arthritis is, however, obvious to even the casual observer, and the chronicity of this syndrome is well known. It is becoming apparent to all that remissions and exacerbations are seen frequently in SLE. In the last few years,

TABLE I. SYSTEMIC LUPUS ERYTHEMATOSUS, ANGIITIS, AND RHEUMATOID ARTHRITIS (DISTINGUISHING FEATURES)

	SYSTEMIC LUPUS ERYTHEMATOSUS	ANGIITIS	RHEUMATOID ARTHRITIS
Characteristic blood vessel involvement	Fibrinoid	Cellular inflammation	Overgrowth of small vessels
Rheumatoid nodule	0*	0†	+
Serologic reaction			
L.E. preparation	+	0‡	0‡
Serologic tests for rheumatoid arthritis	+ 25–60%	+ 40%	+ 70%
Clinical features			
Joint involvement—			
arthralgias	+++	+++	+
chronic deforming arthritis	+	+	+++
Ultraviolet sensitivity	+++	0	0
Renal involvement	++	++	0§
Retinal changes	++	++	0
Skin rashes	++++	++	±
Thrombocytopenia	++	0‖	0
Hemolytic anemia	++	?	±
Constitutional symptoms	+++	+++	+++
Fever	+++	+++	±
Central nervous system lesions	+++	+++	0
Peripheral nerve lesions	++	+++	+

*If one assumes that SLE developing in a patient with florid rheumatoid arthritis represents the appearance of a second disease.

†If one adopts the point of view that malignant rheumatoid arthritis does not represent angiitis.

‡If one accepts the specificity of the L.E. phenomenon.

§In the absence of amyloid.

‖Excluding the possibility that thrombotic thrombocytopenia represents an angiitis.

Trends alone are shown in the table. The scarcity of unqualified zeros is apparent, reflecting the difficulty in making a clear-cut distinction between the three syndromes.

two types of clinical courses have been emphasized in rheumatoid arthritis, the episodic and the sustained.[22] If followed long enough, the "average patient" usually represents a mixture of the two types in various combinations. The development of irreversible damage to the musculoskeletal system may make the assessment of a complete remission difficult. In contrast to this, the vascular lesions of SLE or angiitis may subside leaving no clinically detectable damage

and an apparently complete remission will be observed in a fashion comparable to that seen in acute glomerulonephritis. Thus, on the basis of the average patient, the natural history of the three diseases may show striking differences which may be more apparent than real.

Ultraviolet sensitivity preceding the onset of an acute SLE, particularly but not exclusively its dermatologic manifestations, has been commonly observed. Such a relationship has not been noted to occur in rheumatoid arthritis or angiitis.

Multiple system involvement, i.e., renal, cardiac, pulmonary, central, or peripheral nervous system, should invoke the suspicion of SLE or angiitis rather than rheumatoid arthritis. It is only the exceptional patient with rheumatoid arthritis who develops such systemic manifestations as seen in the malignant form of the disease, and the final distinction in these patients often must wait for histologic confirmation.

OL.
5
957

Skin involvement is more frequently associated with SLE than with angiitis or rheumatoid arthritis. The typical butterfly lesion apparently has become less prevalent since the medical profession has become aware of the high frequency of SLE in the sick population, but when it does develop it must be considered pathognomonic for that disease. The predilection of SLE for young females should arouse a suspicion of this disease when symptoms appear in this age and sex group.

Thrombocytopenia with purpura is seen most frequently in SLE, although some consider the syndrome known as thrombotic thrombocytopenia purpura to be a form of angiitis. In rheumatoid arthritis, thrombocytopenia not related to chrysotherapy is seen commonly only in Felty's syndrome, which represents in essence rheumatoid arthritis with hypersplenism. An hemolytic anemia of a severe degree is also more usually associated with SLE, although there is evidence to indicate that a mild hemolytic component is present in the anemia of certain patients with rheumatoid arthritis.[23] No published information was found to incriminate a hemolytic component in the anemia of angiitis.

The clinical similarities of these three syndromes are many. Joint involvement is characteristically chronic and destructive in rheumatoid arthritis. It is characteristically fleeting and nondestructive in SLE and angiitis, but numerous instances of chronic deforming arthritis have been reported in both SLE and angiitis. In episodic rheumatoid arthritis, the joint lesion need not necessarily be destructive. In palindromic rheumatism which is thought by many to represent a prodromal manifestation of rheumatoid arthritis, one diagnostic criterion is absence of joint damage. Ropes has shown a difference in the synovial fluid hyaluronate in SLE and rheumatoid arthritis.[24] Whether this difference is wholly definitive is not established, since it appears from the protocols that the joint involvement in these patients with SLE was rather acute. We have one patient with chronic rheumatoid arthritis who subsequently developed SLE. The joint fluid removed from her knee on several occasions showed the characteristics of a low-polymer hyaluronate which we have associated with rheumatoid arthritis.

General symptoms of weight loss, fatigue, listlessness, aching, and even muscle stiffness are seen in all three syndromes. Fever of significant degree

is rare in the patient with uncomplicated rheumatoid arthritis. It is seen frequently in SLE and angiitis. Retinal lesions are rarely seen in rheumatoid arthritis. The cytoid body is assumed to be seen only in SLE, but it is difficult for the uninitiated to distinguish this abnormality from an exudate. Hemorrhages may be seen in both SLE and angiitis.

Renal abnormalities, such as hematuria, albuminuria, and azotemia, are commonly observed in SLE and angiitis, but are rare in rheumatoid arthritis in the absence of amyloid. Hypertension is also seen commonly with SLE and angiitis, but in rheumatoid arthritis it seems to parallel the frequency seen in the general population.

Evidence of central nervous system damage, particularly convulsions, seems to be observed clinically more frequently in SLE than in the other two syndromes. Peripheral nerve lesions have been observed in all three disease patterns, possibly more frequently in angiitis.

In certain instances, the clinical picture may be identical, but multiple system involvement points away from rheumatoid arthritis toward SLE or angiitis. The definite distinction between the latter two must rest upon the development of a characteristic clinical lesion for SLE or a positive L.E. preparation if the latter be accepted as a phenomenon pathognomonic of SLE. A diagnosis of angiitis can only be made by exclusion or possibly by a positive biopsy.

VOL 5 195

SEROLOGIC CONSIDERATIONS

Several serologic reactions are associated with these syndromes. Mention has been made above of the L.E. phenomenon. It is our feeling that this is a relatively specific biologic reaction when the technique is rigidly standardized. On the other hand, the serologic reactions seen in rheumatoid arthritis, the streptococcal agglutination, sensitized sheep cell, F II reaction, and precipitin with gamma globulin, are seen rather commonly in all three diseases, rheumatoid arthritis, SLE, and angiitis.[25,26] A rough approximation would be that these are positive in 70 per cent of the patients with rheumatoid arthritis (95 per cent of those with nodules), 25 to 60 per cent of patients with SLE, and 20 to 40 per cent of patients with angiitis. It has been known for a long time that the serum of patients with rheumatoid arthritis may form a spontaneous precipitate on standing, particularly when cooled.[27] This differs from the usual chryoglobulin in that it does not return to solution on warming to 37° C. This phenomenon may also be seen in SLE and in angiitis. True chryoglobulins, which dissolve on warming, have been observed in angiitis.[28] In the past, the precipitin reaction for trichinella was thought to be positive frequently in angiitis but the reaction is too nonspecific to be of much value. Various protein abnormalities such as hyperglobulinemia (Howe method) and elevated gamma and alpha-2 globulins are often seen in each of these three syndromes, the intensity probably depending upon the severity and chronicity of the process. It does seem possible that a positive cephalin flucculation may be observed more frequently in SLE, and a false positive biologic serologic test for syphilis is definitely seen more frequently in SLE than in the other two disease patterns.

SUMMARY

An attempt has been made to describe the relationship between three syndromes which not infrequently present a similar clinical picture and may have in common certain histologic and serologic features. It is not possible at the present time to state whether or not these features indicate similarities in pathogenesis.

Definite distinction between these syndromes is frequently impossible because of lack of knowledge of both pathogenesis and a predictable natural history. In many instances, however, the distinction may be reached on clinical grounds, particularly when multiple systems are involved. Some help may be found in utilizing certain serologic reactions which point the way to an approximation of an accurate diagnosis. An attempt to distinguish between the three syndromes is of importance because of differing prognoses in each and because the philosophy of management suitable to each differs. Hazardous measures which may be lifesaving in an acute phase may be considered when a potentially fatal disease, e.g., SLE or angiitis, needs to be controlled.

VOL.
5
957

REFERENCES

1. Hazerick, J. R.: Evaluation of Three Diagnostic Procedures for Systemic Lupus Erythematosus, Ann. Int. Med. **44**:497, 1956.
2. Dustan, H. P., Taylor, R. D., Corcoran, A. C., and Page, I. H.: Rheumatic and Febrile Syndrome During Prolonged Hydralazine Treatment, J. A. M. A. **154**:23, 1954.
3. Blankenhorn, M. A., Zeek, P., and Knowles, H. C., Jr.: Periarteritis Nodosa and Other Forms of Necrotizing Angiitis: A Clinical and Pathological Correlation, Tr. A. Am. Physicians **66**:156, 1953.
4. Robinson, W. D., and Others: Annual Rheumatism Review, Ann. Int. Med. (In press.)
5. Rich, A. R.: Hypersensitivity in Disease, Harvey Lect. **42**:106, 1946-47.
6. Hawn, C. v. Z. and Janeway, C. A.: Histological and Serological Sequences in Experimental Hypersensitivity, J. Exper. Med. **85**:571, 1947.
7. Moore, J. E., and Lutz, W. B.: The Natural History of Systemic Lupus Erythematosus: An Approach to its Study Through Chronic Biologic False Positive Reactors, J. Chron. Dis. **1**:297, 1955.
8. Short, C. L., and Bauer, W.: Course of Rheumatoid Arthritis in Patients Receiving Simple Medical and Orthopedic Measures, New England J. Med. **238**:142, 1948.
9. Ragan, C.: Rheumatoid Arthritis: The Natural History of the Disease and its Management. Bull. New York Acad. Med. **27**:63, 1951.
10. Sokoloff, L.: Some Aspects of the Pathology of Collagen Diseases, Bull. New York Acad. Med. **32**:760, 1956.
11. Sokoloff, L., McCluskey, R. T., and Bunim, J. J.: Vascularity of the Early Subcutaneous Nodule of Rheumatoid Arthritis, A. M. A. Arch. Path. **55**:475, 1953.
12. Godman, G. C., and Churg, J.: Wegener's Granulomatosis. Pathology and Review of the Literature, A. M. A. Arch. Path. **58**:533, 1954.
13. Bevans, M., Nadell, J., Demartini, F., and Ragan, C.: The Systemic Lesions of Malignant Rheumatoid Arthritis, Am. J. Med. **16**:197, 1954.
14. Harvey, A. McG., Shulman, L. E., Tumulty, P. A., Conley, C. L., and Schoenrich, E. H.: Systemic Lupus Erythematosus. Review of the Literature and Clinical Analysis of 138 Cases, Medicine **33**:291, 1954.
15. Klemperer, P., Gueft, B., Lee, S. L., Leuchtenberger, C., and Pollister, A. W.: Cytochemical Changes of Acute Lupus Erythematosus, Arch. Path. **49**:503, 1950.
16. Godman, G. C., Deitch, A. D., and Klemperer, P.: On the Composition of the Hematoxylin Bodies of Systemic Lupus Erythematosus, Am. J. Path. **32**:616, 1956.
17. Sokoloff, L., Wilens, S. L., Bunim, J. J., and McEwen, C.: Diagnostic Value of Histologic Lesions of Strated Muscle in Rheumatoid Arthritis. Am. J. M. Sc. **219**:174, 1950.
18. Robinson, W. D., French, A. J., and Duff, I. F. Polyarteritis in Rheumatoid Arthritis, Ann. Rheumat. Dis. **12**:323, 1953.
19. Cruickshank, B.: The Arteritis of Rheumatoid Arthritis, Ann. Rheumat. Dis. **13**:136, 1954.
20. Gruenwald, P.: Visceral Lesions in a Case of Rheumatoid Arthritis, Arch. Path. **46**:59, 1948.
21. Ragan, C., and Snyder, A.: Rheumatoid Arthritis, Disease-a-Month, Chicago, 1955, Yearbook Publishers, Inc.

22. Short, C. L., Reynolds, W. E., and Bauer, W.: Rheumatoid Arthritis With Remissions: A Study of 80 Patients, Ann. Rheumat. Dis. **13**:362, 1954.
23. Ebaugh, F. G., Jr., Peterson, R. E., Rodnan, G. P., and Bunim, J. J.: The Anemia of Rheumatoid Arthritis, M. Clin. North America **39**:489, 1955.
24. Ropes, M. W., and Bauer, W.: Synovial Fluid Changes in Joint Disease. Cambridge, 1953, Harvard University Press.
25. Jessar, R. A., Lamont-Havers, R. W., and Ragan, C.: Natural History of Lupus Erythematosus Disseminatus, Ann. Int. Med. **38**:717, 1953.
26. Jacobson, A. S., Kammerer, W. H., Wolf, J., Epstein, W. V., and Heller, G.: The Hemagglutination Test for Rheumatoid Arthritis: III. Clinical Evaluation of the Sheep Erythrocyte Agglutination (S. E. A.) Test and the Gamma Globulin (F II) Tests, Am. J. Med. **20**:490, 1956.
27. Chasis, H., and McEwen, C.: Precipitin Reactions Between Hemolytic Streptococci of Various Groups and Immune and Rheumatoid Arthritic Sera, J. Immunol. **31**:439, 1936.
28. Lepow, H., Rubenstein, L., Woll, F., and Greisman, H.: A Spontaneously Precipitable Protein in Human Sera, With Particular Reference to the Diagnosis of Polyarteritis Nodosa, Am. J. Med. **7**:310, 1949.
29. Ball, J.: Rheumatoid Arthritis and Polyarteritis Nodosa, Ann. Rheumat. Dis. **13**:277, 1954.
30. Skogrand, A.: Visceral Lesions in Rheumatoid Arthritis, Acta rheumat. scandinav. **2**:17, 1956.

CONSERVATIVE THERAPY IN RHEUMATOID ARTHRITIS

MARIAN W. ROPES, M.D.

BOSTON, MASS.

From the Medical Clinic of the Massachusetts General Hospital, the Department of Medicine, Harvard Medical School and the Massachusetts Department of Public Health

(Received for publication Feb. 5, 1957.)

VOL. 5 1957

RHEUMATOID arthritis remains a disease of unknown etiology and of varied manifestations involving almost all systems of the body. The course, similarly, varies to a marked degree from patient to patient and in individual patients. The tendency for unpredictable spontaneous remissions and exacerbations makes it extremely difficult to evaluate the results of any treatment.

The ability of ACTH and cortisone to reduce dramatically the symptoms and signs of rheumatoid arthritis has been unequivocally demonstrated. Hydrocortisone, prednisone, prednisolone, and other steroids have a similar effect. Despite the dramatic anti-inflammatory action of these agents, however, we are without evidence that they alter fundamentally the natural course of the disease. In fact, continued progression of disease, as demonstrated by increased x-ray changes, is known to occur and in the majority of patients there is no indication that any healing can be attributed to hormone therapy. Similarly, in the case of the many other suggested treatments, no evidence of any true curative effect has been adduced and continued progression of disease has been noted in many patients. These treatments include gold and butazolidine and also those of more questionable symptomatic value: vitamin D in massive doses, the combination of desoxycorticosterone acetate and ascorbic acid, pregnenolone, Prostigmine, cobra venom, bee venom, removal of foci of infection, vaccines, sulfur, copper, thiouracil, placental "serum," post-partum blood, antimalarials, and nitrogen mustard. Furthermore, with some of these forms of treatment, including steroids, the attendant risks are great and may increase with use of the medication in high doses or for a long period of time. Whether such risks are warranted, in the absence of demonstration of curative value of the treatment, must be decided in each individual case.

Even if we did have a "specific" therapy, i.e., one that produces complete reversal of all manifestations of the disease, many features of the so-called conservative program would still be indicated and, in the absence of any such therapy, this program becomes of major importance. The rationale of such a regime

This is publication No. 210 of the Robert W. Lovett Memorial Foundation for the Study of Crippling Diseases.

The expenses of this investigation have been defrayed in large part by a grant from the Commonwealth Fund with additional support from the United States Public Health Service.

is to care for the inflamed joints in such a manner as to decrease inflammation and preserve function, and if possible to increase the patient's resistance and support. The value of such therapy in improving joint and muscle function is without question, but whether or not it alters the course of the disease is as difficult to determine as in the case of any of the treatments mentioned above, because of the extreme fluctuations in the natural course of the disease.

Attempts to prove the value of such a regime on the basis of statistical evidence have been unsuccessful. Such difficulty might be expected in the case of a disease in which accurate diagnosis is difficult; the course in individual patients is entirely unpredictable; and the determination of the degree of activity of the disease in any patient at any definite point in time is unsatisfactory. Since it is often impossible even in any one patient to determine whether or not a treatment has reduced the activity of the disease, it is obviously, therefore, equally impossible to state accurately the percentage of patients improved by any course of therapy. The similarity in the percentage of patients who show improvement under a great variety of treatments is merely the expression of this difficulty in evaluation, and may well represent the natural course of the disease.

Careful follow-up studies have been carried out in three groups of patients in an attempt to determine the course of the disease under the conservative regime. A series of 250 unselected patients receiving simple medical and orthopedic measures were observed by Short and Bauer[1] for an average of 9½ years with a range of 6 months to 16 years. When reported, 53 per cent were in remission or definitely improved. In a similar series of 374 patients followed by Ragan[2] from 5 to 20 years with an average of 11 years, 48 per cent were in remission or markedly improved. More recently in a series of 282 patients followed by Duthie[3] for a shorter interval (an average of 2 years), 71 per cent were classified as improved or markedly improved. In terms of the percentages of patients in remission or markedly improved, (48 to 71 per cent) these results compare favorably with those reported by various workers after treatment with gold or hormones.[4-10] However, the difficulty in evaluating the percentage of patients improved after any therapy has already been discussed. It cannot at present be proved statistically that the conservative regime, or any other therapy, alters the natural course of the disease. Conclusive evidence on this point would be of utmost value. In its absence one can merely discuss the various aspects of the regime and their apparent value.

Only by following many patients over long periods of time can one estimate empirically the role of the conservative regime. As stated above the objective of this regime is to decrease joint inflammation and prevent or lessen deformities. Involved in this objective are the reduction of wear and tear on inflamed joints, maintenance of optimum position of joints, and improvement of function of joints and muscles by salicylates, exercises, and heat. There is adequate proof of the value of these aspects of conservative therapy, but evidence is more tenuous in regard to the other objectives, namely, the improvement of the general condition of the patient and the aiding of any natural forces that combat the disease.

However, the decrease in systemic symptoms and clinical and laboratory signs of active disease which follows initiation of this program is often extremely impressive. Whether or not there is, in addition, an actual anti-inflammatory effect of the commonly employed drugs, aspirin, or other salicylate, is not known. The close similarity in results obtained with aspirin to those with the known anti-inflammatory agents (cortisone and ACTH) in the treatment of both rheumatic fever and rheumatoid arthritis[11-14] suggests that there is, in addition to an analgesic effect, a suppression of the inflammation. Similarly, clinical experience with the dramatic immediate changes produced by administration of aspirin in many patients with rheumatic fever and in some with rheumatoid arthritis, and with the exacerbations that may be produced by withdrawal of aspirin in such cases also suggests an anti-inflammatory action. However, there is as yet no convincing proof of such an effect.

VOL.
5
1957

The features of the regime that are generally accepted to be of value are: rest; support of the patient in every way possible (emotional, social, environmental, and economic); salicylates; exercises; heat in various forms; physical support of joints; and adequate intake of protein, minerals, and vitamins.

Rest.—The fundamental importance of bed rest combined with generalized active exercises to maintain and improve joint and muscle function and prevent any ill effects of continued rest is well recognized despite the absence of any proof of its value. The amount of rest and the duration of the period of increased rest must be decided for each patient. In severe, active disease complete bed rest is desirable, even without lavatory privileges if the situation permits. Such a regime is, in fact, essential in acute, febrile cases with severely inflamed joints (often resembling those of specific infectious arthritis or rheumatic fever), and in patients in whom the disease is rapidly progressive or those with marked constitutional manifestations. In some patients the weight-bearing joints are so deformed or so acutely inflamed as to make walking impossible or unwise. Such a rest regime should be prescribed, however, even though weight-bearing joints are not involved, since it is rest of the patient as a whole that is essential. The tendency for the feeling of stiffness that follows periods of rest (the "gelling" phenomenon) to be more apparent at first after the initiation of such a regime is not a contraindication. Such stiffness is not followed by increased limitation of function, and tends to subside as the regime is continued and the activity of the arthritis decreases. Unfortunately, it is the overconcern for such stiffness that leads many patients and their physicians to decry bed rest and push activity despite increasing fatigue and pain. In less severe disease, less rest is necessary. The criterion for adequate rest in any one patient, and the empirical evidence for its value, is the overcoming of constitutional symptoms, such as fatigue, and the subsidence of other evidences of activity of the arthritis. In mild cases, it is often possible for patients to continue their work with the addition of 2 to 4 hours of rest each day with reduction of fatigue and slow improvement in their arthritis. In moderate cases, complete bed rest may not be necessary but varying amounts of rest must be prescribed, ranging from 10 to 12 hours in bed at night with one or two rest periods during the day, to bed rest from 18 to 20 hours out of the 24.

The duration of bed rest will depend upon the response in each case. The prescribed amount of rest is continued, with the other treatments discussed below, until signs and symptoms of the disease have disappeared or, after improving, have remained at a constant level for at least 6 to 8 weeks. The improvement must not be merely in the functional state of the patient but must include lessening or disappearance of the signs of activity of the disease, such as weight loss, joint swelling, elevated sedimentation rate, and lowered hemoglobin concentration. The process of getting up must be gradual. In patients who have been at complete bed rest, sitting for 10 to 15 minutes in a chair is all that should be allowed at first. Activity is then increased slowly, an increment being added only when any effect of the last increase, especially any fatigue, has subsided.

Emotional Support.—Of equal or greater importance than bed rest is the need to help the patient attain the maximum degree of composure and adjustment to his life's problems. This necessitates appreciation of the personality of the patient and as full knowledge as possible of the emotionally disturbing factors present before the onset of the disease and enhanced, or increased in number, by the painful, disabling illness. This approach requires much time as well as patience, true belief, ingenuity, and equanimity on the part of the physician. With most of the patients it is difficult to lead them into a discussion of material that is emotionally significant. Only slowly, through many conversations related to family, friends, interests, activities, fears, ideals, etc., can one obtain knowledge of the emotional factors that may have played a role in the precipitation of arthritis, or even more likely, may have hindered the healing and allowed increased progression of the disease. Since psychiatric evaluation and care is either not available or necessarily advisable for every patient with rheumatoid arthritis, some form of psychotherapy must be offered by the physician treating the patient. This must include an attempt to help the patient accept the importance of the emotional factors and their role in the precipitation or prolongation of the illness. For, if this concept is accepted, the solution of emotional problems or the lessening of reaction to them becomes to the patient an important part of the treatment; cooperation is more wholehearted; the relationship between patient and doctor more satisfying; and progress is more rapid.

Adequate emotional support requires careful consideration of the social, environmental, and economic factors. Of inestimable value in this program is the medical social worker, when available. One of the immediate problems is the decision as to where the treatment involving so much bed rest should be carried out. There is little question that the regime is usually easier to follow and more successful in a hospital than at home, even though the latter may have adequate facilities for care. The reasons for this difference are often hard to determine, but they include the difficulties for the patient: of being an invalid (often not appearing ill) in a group of well individuals; of having inadequate support in following the regime; of being in the center of emotional tensions and situations that may have been actual precipitating factors for the arthritis; of taking part, from the bed, in too many activities with family or visitors; of being

too dependent or too hostile and unable to express feelings freely. The superiority of hospitalization over home care in many patients is best demonstrated by the improvement that frequently occurs immediately after admission to the hospital even though no other change in regime is made. However, despite the advantages of prolonged hospitalization for full adherence to the regime, few facilities are available for long-term care of patients with arthritis. Furthermore, any hospitalization adds financial problems which enhance those already present, and for this reason alone hospitalization is not feasible in many patients. In such cases, rearrangement of the home, with increased help and often removal of people dependent on the patient for care, involves careful planning. The importance of each aspect of the total regime must be explained not only to the patient but to all members of the household. It should be clearly understood that, if evidence of progress is not definite in 4 to 6 weeks, hospitalization must be arranged.

VOL.
5
1957

The question of vocational rehabilitation is outside the limits of this article and is discussed elsewhere in this issue. It represents a major emotional problem for some patients. In so far as is possible, decision should be made early in the course of treatment as to whether the patient will be able to return to his or her former living arrangements and occupation and, if not, what the other possibilities are. Only in this way can there be a positive attitude and planning for the future which is essential as an incentive to the patient and a requisite for subsidence of the disease. If such incentive does not develop, direct challenging as to the reasons for the lack of desire to get well and the necessity for such a stimulus may be advisable and of great value in selected patients. Such an approach will often include a discussion of the emotional value of the illness to the patient (usually subconscious); the possible welcoming of sickness as a form of adjustment; reduction, or absence of satisfactions at the time of onset of the disease; and lack of visualization of adequate satisfactions in the future to act as an incentive. Success in this approach will depend on the extent to which the patient grasps the importance of emotional factors in the subsidence of the disease and on the soundness of the reasons he gives for wanting to get well.

Salicylates.—As a prerequisite for physical and emotional rest, the relief of pain is of paramount importance in the treatment of rheumatoid arthritis. Aspirin is still the drug of choice and should be given in full doses. In general, especially when patients are under observation, it is wise to determine the limit of tolerance. Either 0.6 Gm. every 2 hours or 0.9 Gm. every 3 hours should be given day and might until tinnitus appears. Aspirin is then discontinued until the ringing has disappeared, and, on resumption, the total 24-hour dose should be 0.6 to 0.9 Gm. less than the amount that produced tinnitus. Daily doses of 5 to 6 Gm. or more are often required. Older people tolerate the drug less well, whereas children can tolerate a relatively larger dose than most adults. In milder cases, smaller doses may be adequate to remove pain and spasm, and allow good joint and muscle function. Three to four grams, however, are usually necessary. In general, 0.6 Gm. every 2½ to 3 hours, with the first dose as early in the morning as possible, seems effective, though some prefer larger doses at longer intervals. The latter may increase gastric irritation. Aspirin should be

given regularly at a constant dose and not decreased or omitted because of temporary subsidence of symptoms; nor should the patient be allowed to vary the dose at will. Full doses should be continued until the patient has been free of signs of disease activity and of joint symptoms, even on full motions, for at least 6 to 8 weeks, or for a longer period in severe cases. The dose is then decreased slowly, with resumption of the original level if signs or symptoms recur.

Aspirin is not only efficacious in the relief of pain but is relatively safe. At therapeutic levels the chief hazards are gastric irritation, occasionally with bleeding; tinnitus; and deafness. Fortunately, gastric irritation can be avoided in almost all instances by the use of one of the many tablets in which aspirin is enteric coated or buffered by aluminum or magnesium hydroxide or calcium glutamate. Rarely, a patient is unable to take full doses of aspirin, even protected, without gastric symptoms. Substitution, in part or wholly, by sodium salicylate (in the absence of hypertension or congestive failure) or by Phenacetin (up to 2 Gm. a day) will often be of symptomatic value and will usually remove the gastrointestinal symptoms. Tinnitus should be controlled by lowering of the dose. Any loss of auditory acuity is an indication for temporary discontinuance of the drug and resumption at a slightly lower level in order to prevent the possibility of irreversible deafness. Toxicity should be watched for most carefully in patients with limited renal function or with high fever associated with poor fluid intake or vomiting. Hyperpnea, mental confusion, lassitude, or drowsiness will suggest the presence of toxicity, and are usually associated with nausea and vomiting that are central in origin in contrast to the gastrointestinal symptoms from local gastric irritation that appear even with therapeutic doses as described above. Significant lowering of prothrombin concentration, with hemorrhagic phenomena, occurs with severe toxicity.

In general, the dose of aspirin is best regulated by the response of the patient and the limit of tolerance as described above. In some instances, however, determination of the salicylate level in the plasma may be indicated. The chief value will be in discovering the occasional patient in whom the level remains very low (below 10 or 15 mg. per 100 c.c.) on a relatively large dose. However, the ideal plasma concentration for therapy is not known. Apparently it varies considerably with age and may be as low as 15 mg. per 100 c.c. in older people, as high as 40 mg. in children, and approximately 25 mg. in young adults. Until the significance of the level, the best analytical method, and the form in which salicylates are active therapeutically are known, plasma levels will remain of limited value clinically.

Aspirin is employed for its analgesic action. The relief of pain and muscle spasm permits more normal joint motions and tends to prevent deformities. Whether or not aspirin has also an anti-inflammatory action is not known, as discussed above. However, in view of the suggestive evidence of such an effect, it is advisable to administer aspirin in full doses to all patients, including severe cases with marked systemic involvement such as pericarditis and myocarditis, even though pain is not present.

Physical Therapy.—Detailed discussion of the use of physical therapy is not within the scope of this article and is discussed elsewhere in this issue but it is

important to emphasize its value. From the very beginning of treatment active exercises, or if necessary passive supported movements, within the limits of pain, are essential, both to prevent adhesions and to preserve, in so far as possible, joint and muscle function. Active exercises throughout treatment should, in general, be limited not by fatigue and pain occurring *during* but that persisting *after* exercises. Such exercises should be generalized during the period of bed rest, and should at all times include all joints which are involved to any degree. The frequent application of heat also leads to improved function and lessened deformity. There is no proof that any form of heat is superior to another, though there is a clinical impression that moist heat is preferable.

Support of Joints.—Along with rest of the individual, rest of the involved joints promotes the subsidence of inflammation. No weight-bearing or excessive use should be permitted with acutely inflamed joints or those with weak muscles. Support of joints by splints in optimum position leads to improved function and lessened deformity by protecting against the deforming influences of muscle spasm and gravity. Since inflamed joints usually are held in flexion, support in such cases is applied with the joint in as much extension as possible. Mild sedation for the application of the cast is of value in allowing extension, but it is inadvisable, in general, to aid extension by anesthesia since, with recurrence of spasm, it will be impossible for the patient to wear the cast with comfort. Manipulation under anesthesia, with forced extension of the joint, is contraindicated because of actual tearing of tissues with resulting bleeding and increased inflammation. Improvement in position gained by wearing casts does not arise from any pressure forcing the joint into extension, but rather from complete support which leads to relaxation of spasm and resulting extension. The joints for which splints are most effective are knees, wrists, and spine. In some cases, elbow casts are satisfactory but, in general, they require careful fitting to be comfortable and to provide adequate support to lessen spasm. Casts for the legs should be bivalved and inclusion of the foot is essential for adequate relaxation. In the case of cock-up splints for the wrists, only a palmar splint is necessary, except in severe cases. The cast need extend only to the middle of the palm if phalangeal joints are not involved. When ulnar deviation is present, the support should extend to the finger tips, and ridges should be incorporated to hold each finger as near the neutral position as possible. Plaster shells for support of the back should extend only to the mid-thoracic region, thereby allowing extension of upper dorsal region above the cast. Casts should be worn for 10 to 12 hours at night and, with severe deformities, for at least 2 periods of 3 hours each during the day. The danger of immobilization in splints without removal at least 3 times a day for heat and exercises cannot be emphasized too greatly. The tendency for periarticular and intra-articular fibrous adhesions to form is ever present and makes it essential that joints be put through the full range of movement that is possible several times a day. Limitation of motion of considerable degree may occur rapidly, and, on rare occasions, in acutely inflamed joints, permanent ankylosis has been produced by complete immobilization for as short a period as 2 to 3 weeks.

Traction, with reduction of muscle spasm, is also of value in improving function and lessening deformity, especially in the case of knees, hips, and neck.

VOL.
5
1957

The latter can be applied for 2 or 3 periods a day with the patient in the bed or, preferably, sitting in a chair. Traction for knees or hips should be maintained throughout the day and night with the exception of periods for exercises and application of heat.

Surgical Procedures.—While surgical procedures are not strictly a part of the conservative treatment of rheumatoid arthritis, they sometimes form a valuable adjunct to this regime and aid in the improvement of function and control of pain. Mention should be made of the benefit obtained from metatarsophalangeal joint resections, elbow arthroplasty, or fusion of wrist or ankle in carefully selected patients. We shall continue to favor the use of cup arthroplasty[15] in the treatment of hip deformity unless it is eventually proved that femoral head prostheses produce more favorable results and fewer complications.

Diet.—Patients with rheumatoid arthritis have long been subject to varying forms of dietary restrictions or imbalance. However, there is no evidence that any food or class of foods is in any way harmful or that any alteration of a normal diet is of value. Furthermore, no proof of any dietary dificiency has geen found, despite the demonstration of low plasma levels of vitamins A and C. On empirical grounds, it is generally agreed that a patient with rheumatoid arthritis should receive a well-balanced diet that is more than adequate in every respect, with the calories adjusted to the patient's energy requirement and weight. Adequacy of proteins, calcium, phosphorus, iron, and vitamins is of importance. The addition of extra vitamins is not necessary if such an adequate diet is actually taken. Iron is of little value in treatment of the anemia during active disease, but, as activity subsides, it may aid in restoration of a normal hemoglobin level in patients in whom the presence of iron deficiency is shown by the serum iron level. Transfusion of whole blood is indicated in patients with severe anemia. In occasional cases the excellent response might suggest an action in addition to increase in hemoglobin concentration, but no such action has been proved. In any event, the use of transfusions in severely ill patients with marked anemia seems warranted despite the hazard of homologous serum jaundice.

Essential to this entire program is a belief on the part of the physician that rheumatoid arthritis is reversible, at least in part, in a large majority of patients. Without this belief in a remission it is obviously impossible to help the patient adhere to any regime or have faith in the outcome. Equally essential is the realization that the time required for remission varies from weeks to years and that there is as yet no way to determine the time required for remission in any one patient. It is, therefore, impossible to "set any date," even approximately, for the occurrence of remission. Acceptance of this fact will often prevent the recurrent periods of discouragement on the part of the patient and the recurrent need on the part of the physician to do something more dramatic.

The importance of the basic treatment that comprises the "conservative regime" is generally accepted. There is, however, no proof that it alters the natural course of the disease, and, unfortunately, despite the immeasurable value of such proof, it is unlikely that it can be obtained until better criteria for diag-

nosis, greater predictability as to course, and accurate measurement of the state of activity of the disease are available. On the other hand, one can feel confident that the conservative program, if faithfully carried out, will decrease the crippling due to an attack of rheumatoid arthritis. In addition, an impressive decrease in symptoms and signs of active disease often follows the initiation of this program. Whether this reflects a true decrease in disease activity and indicates a shortening of the duration of disease activity by the treatment are questions which cannot yet be answered.

REFERENCES

1. Short, C. L., and Bauer, W.: The Course of Rheumatoid Arthritis in Patients Receiving Simple Medical and Orthopedic Measures, New England J. Med. **238**:142, 1948.
2. Ragan, C.: The General Management of Rheumatoid Arthritis, J.A.M.A. **141**:124, 1949.
3. Duthie, J. J. R., Thompson, M., Weir, M. M., and Fletcher, W. R.: Medical and Social Aspects of the Treatment of Rheumatoid Arthritis, Ann. Rheumat. Dis. **14**:133, 1955.
4. Short, C. L., Beckman, W. W., and Bauer, W.: Gold Therapy in Rheumatoid Arthritis, New England J. Med. **253**:404, 1955.
5. Ragan, C., and Tyson, T. L.: Chrysotherapy in Rheumatoid Arthritis, Am. J. Med. **1**:252, 1946.
6. Ragan, C.: Rheumatoid Arthritis. The Natural History of the Disease and its Management, Bull. New York Acad. Med. **27**:63, 1951.
7. Howell, D., and Ragan, C.: The Course of Rheumatoid Arthritis During Four Years of Induced Hyperadrenalism, Medicine **35**:83, 1956.
8. Bunim, J. J., Ziff, M., and McEwen, C.: Cortisone Therapy in Rheumatoid Arthritis: A Four-year Appraisal, Bull. Rheumat. Dis. **5**:73, 1954.
9. Hansen, K. B., Fischer, F., and Brochner-Mortensen, K.: Treatment of Rheumatoid Arthritis With Cortisone (Two- to Four-year Studies), Acta rheumat. scandinav. **1**:7, 1955.
10. Solem, J. H., and Römcke, O.: Clinical Evaluation of Prolonged ACTH and Cortisone Therapy in 114 Cases of Rheumatoid Arthritis, Acta rheumat. scandinav. **1**:243, 1955.
11. Medical Research Council and Nuffield Foundation. A Comparison of Cortisone and Aspirin in the Treatment of Early Cases of Rheumatoid Arthritis, Brit. M. J. **2**:695, 1955.
12. Empire Rheumatism Council. A Multi-centre Controlled Trial Comparing Cortisone Acetate and Acetyl Salicylic Acid in the Long-term Treatment of Rheumatoid Arthritis, Ann. Rheumat. Dis. **14**:353, 1955.
13. Ansell, B. M., Bywaters, E. G. L., and Isdale, I. C.: Comparison of Cortisone and Aspirin in Treatment of Juvenile Rheumatoid Arthritis, Brit. M. J. **1**:1075, 1956.
14. Medical Research Council and American Heart Association. Joint Report by the Rheumatic Fever Working Party of the M.R.C. and the Subcommittee of Principal Investigators of the American Council on Rheumatic Fever and Congenital Heart Disease, Brit. M. J. **1**:555, 1955.
15. Smith-Petersen, M. N.: Arthroplasty of the Hip, J. Bone & Joint Surg. **21**:269, 1939.

VOL.
5
1957

PHYSICAL THERAPY IN RHEUMATOID ARTHRITIS

JAMES W. RAE, JR., M.D., AND LEONARD F. BENDER, M.D.

ANN ARBOR, MICH.

From the Department of Physical Medicine and Rehabilitation, Medical School, University Hospital, University of Michigan

(Received for publication Feb. 5, 1957.)

IN SPITE of new discoveries and advances in the treatment of rheumatoid arthritis, the most important part of the management of patients with this disease today is the prevention or minimizing of deformity and the maintenance or improvement of function. The numerous remedies that have been promoted for use in arthritis tend to detract from the appreciation of the value of physical treatment in preventing crippling and disability. Hill and Holbrook[1] have estimated that not one patient in 100 is following a proper schedule to protect his joints and maintain function. This is a serious indictment of our medical care programs for patients with rheumatoid arthritis. Whether one agrees with these figures or not, all will agree that a high percentage of patients fail to carry out any program, or go at it halfheartedly, or eventually tend to lose interest in even a carefully planned and effective schedule of treatment.

A review of the literature from 1940 to the present offers little information as to the best way to motivate a patient with a chronic ailment to treat himself over a long period of time. In 1943, a report from the Mayo Clinic[2] gave the results of a survey of arthritis patients chosen at random from several thousand clinic patients who had been instructed in home physical therapy. Of the 346 patients to whom the investigators sent a questionnaire, 216 responded, and the results showed that 92.7 per cent had started the treatment program and 64.7 per cent had continued treatment for three months or more. There were 96 patients with rheumatoid arthritis in this group; 63.5 per cent of these were continuing home treatment or else had stopped because their condition had improved.

A survey of arthritis patients at University Hospital was recently conducted to help evaluate our program of instruction in home treatment and shed some light on why patients continue or stop their home treatment schedules. Fifty-six patients who had previously been instructed in adequate home programs were personally interviewed. At the time of the interview, 5 patients had stopped their home treatment because of improvement in their condition. Of the remaining 51 patients, 27 were still continuing adequate home treatment programs, but 24 patients who needed physical therapy were not treating themselves adequately.

Six of these 24 patients never started on their recommended home program; 8 stopped home treatment between 2 and 4 months after their instruction. This was greater than the number stopping in any other comparable period of time.

There are various factors contributing to the frequent failure to adequately utilize physical treatment in the management of rheumatoid arthritis. Some of these are personal concerns of the patient, situations in which the physician may offer counsel but which otherwise are beyond his control. But even the most ideally situated and motivated patient will fail in treatment if his physician has failed to understand and convey the importance of established principles of care, or has provided inadequate prescription of physical measures, improper scheduling of activities, inadequate instruction of the patient, or inadequate follow-up care and evaluation.

VOL.
5
1957

Basic Principles of Care.—Every physician who assumes the responsibility of caring for the patient with rheumatoid arthritis should recognize the need for establishing a program of symptomatic, constitutional, and supportive measures designed to relieve pain, prevent or minimize deformity, preserve or increase joint range and muscle strength, and maintain or improve functional capacity. Physical treatment consisting of heat, massage, and therapeutic exercise has proved valuable in attaining these goals. To be most effective, physical therapy must be combined with the other established principles of care such as increased general rest, adequate local rest of the involved joints, avoidance of strain and irritation of the involved joints, intelligent use of splints, supports, shoes, and other medical agents (steroids, gold salts, etc.), and surgical procedures as indicated. Daily home treatment prescribed and supervised regularly by a physician familiar with the physiologic effects of physical measures is an essential part of an adequate treatment program for individuals with rheumatoid arthritis. Too frequently in the clinic we see patients who have had courses of steroid therapy or other medical management without ever having been instructed adequately in a consistent and logical home physical treatment regime. The physician must realize the importance of a comprehensive approach in the treatment of rheumatoid arthritis.

Prescription of Physical Measures.—All too frequently, physicians will send patients to the physical therapist without a prescription other than a request for "physio." The therapist is expected to choose the treatment procedures and to establish his own objectives. In effect, this leads to the practice of medicine by the physical therapist, who has had only limited medical training. A vague or muddled prescription is of little more help to the physical therapist. Another form of vagueness is the "shot-gun" type of prescription which may do nothing more than reveal the physician's lack of knowledge of the proper application of physical agents. No therapeutic measure should be prescribed unless there is a specific reason for its use. Routine prescription of heat, massage, and exercise should be avoided. To obtain the most effective use of physical agents in the treatment of arthritis, the physician should provide the same carefully considered and accurately written prescription for physical procedures that he would for drugs.

No prescription for physical therapy is complete if it does not provide the physical therapist with the following minimum information[3]: (1) diagnosis; (2) parts to be treated; (3) specifications regarding procedures or at least the major objectives desired; (4) special instructions regarding anesthetic areas, areas of circulatory embarrassment, removal of dressings, splints, etc.; (5) number and frequency of treatments; (6) date for re-examination by the physician; (7) outline of home instructions, if indicated.

When physical therapy is indicated, any unnecessary delay in starting the treatment may affect the results. In general, the earlier the treatment can be started, the more effective it will be. Also, if the treatment is of real value, it is worth carrying out daily; poor results from physical therapy often occur when treatments are too infrequent. In many cases the treatments should be given twice daily to achieve the most rapid and effective results. Frequent evaluation of the patient's condition is necessary in order to decide whether to continue, discontinue, or alter the treatment program; obviously, therefore, the physician should not lose contact with the patient who is treated by the physical therapist or who is carrying out a home program.

The intelligent use of physical measures and agents requires that the physician have a working knowledge of their physiologic effects. In arthritis, heat is used for its analgesic, muscle relaxing, and vasodilating effects. Massage when properly applied can increase the venous blood flow or lymph flow but is used primarily for its sedative and muscle relaxing effects. Therapeutic exercises employed in arthritis are designed to increase the range of motion of joints or to increase the strength and endurance of muscles. Exercise is the most important part of the physical therapy program.

Listed below are those physical measures most commonly used in the treatment of rheumatoid arthritis along with pertinent remarks regarding their proper application.

Hubbard Tank or Tub Bath:

Employed for general heating
Temperature of water—100° to 104° F.
Duration—15 to 30 minutes
Frequency—daily or every other day
Contraindicated or used with caution in the aged and debilitated

Luminous Bakers:

Used when there is multiple joint involvement; double bakers for general heating
Used at a distance producing a comfortable warmth
Duration—30 minutes
Frequency—one or two times daily
Intensity modified if there is debility, poor circulation or anesthetic area

Infrared Lamps:

Suitable for heating single joints
Used at a distance producing a comfortable warmth
Duration—30 minutes
Frequency—1 or 2 times daily
Intensity modified if there is poor circulation or anesthetic area

Whirlpool Baths:

Effective for heating of multiple joints of upper or lower extremities
Water temperature—105° to 110° F.
Duration—30 minutes
Frequency—daily
Water temperature lowered to 100° F. or less if circulation is impaired

Contrast Baths:

Used when hands or feet are afflicted
Extremity is placed in hot water (105° to 110° F.) for ten minutes, after which it is placed alternately in the cold water (65° to 70° F.) for one minute, then for four minutes in the hot water for several alternations, ending in the hot water
Duration—30 minutes
Frequency—1 to 2 times daily
Temperature of water modified if painful

Paraffin Bath:

Effective method for heating hands and wrists, can be used for feet, can be painted on rounded regions of the body as a pack
Paraffin (5 lb.) melted in a double boiler, add ½ cup of mineral oil, allow to cool until a thin film is formed; hand dipped into paraffin several times until a thick coat is formed, then wrapped in a towel
Duration—20 to 30 minutes
Frequency—1 or 2 times daily
Contraindicated if there is an open wound

Hot Packs:

May be employed for heating regions of the trunk as well as the joints of the extremities.
Woolen material wrung out of hot water (120° F.) and placed over affected joints and changed every 10 to 15 minutes; or commerically available silica gel packs wrapped in turkish toweling and applied to the part
Duration—30 to 45 minutes
Frequency—1 or 2 times daily
Contraindicated if there are areas of anesthesia

Short Wave Diathermy, Microwave Diathermy, Ultrasound:

Heat localized regions well but rarely adaptable to safe home use
Pancake, drum, or wrap around coil techniques are the most effective short wave diathermy applications; microwave diathermy applied at 60 to 80 per cent output; ultrasound intensity 0.5 to 1.5 watts/cm.^{2} using stroking technique
Duration—30 minutes for short wave and microwave diathermy; 5 to 10 minutes for ultrasound
Frequency—daily
These more potent, deep heating agents should be utilized only by qualified professional persons

Massage:

Stroking and kneading movements applied to soft tissues adjacent to the involved joints, *not* to the joint
Mechanical apparatus is not recommended as a substitute
Ordinarily follows use of heat and precedes exercises to increase range of motion

VOL.
5
957

Intensity of the massage depends on degree of inflammatory reaction in joints and tolerance of the patient
May be employed at home by a member of the patient's family who has been instructed in a few simple massage strokes
Not to be employed over areas of infection or malignancy
Not to be used as a reducing procedure, a method for strengthening muscles, or as treatment for psychoneurosis

Therapeutic Exercise:

Most important single physical measure
Active-assistive type of exercise is used to maintain or increase the range of motion of involved joints
Mobilization exercises should be slow, rhythmical, and through the fullest range possible
Purposeless wiggling of the joints should be avoided
Several short periods of exercise daily are better than one long period
Pain lasting more than two hours after exercise indicates that the exercise was too vigorous
Muscle-setting exercises can be utilized to help preserve the strength of large muscle groups, such as hip and knee extensors
Progressive resistive exercises are the most effective in improving strength
Special apparatus may be used, such as weights, exercise table, overhead pulley, shoulder wheel, finger ladder, exercise bicycle, and powder board
Training in posture may improve body mechanics and reduce strain in involved joints
Gait training with or without crutches or canes may be an important part of the exercise program

The Schedule of Activity.—Every patient with rheumatoid arthritis should be placed on a schedule of activity which provides a balance between rest and exercise. Extra rest prevents and minimizes general fatigue and benefits affected joints. Many times inflammation will subside when joints are rested and properly splinted, and strain is removed. The optimal daily average of rest in bed is 10 to 12 hours, but during exacerbations 12 to 24 hours may be indicated. If the patient is not properly instructed he is likely to assume a flexed position in bed. In order that a patient may rest in correct position a firm flat bed is required. It is not rest *or* exercise, but rest *and* exercise.

Instruction of Patient.—Even when the physician does use those measures which have proved to be of value in the management of the patient with rheumatoid arthritis, the patient often will not follow the advice given for home treatment. The physician plays a large role in motivating the patient to carry out an adequate treatment program. It is easier to outline a treatment program than it is to prepare the patient to carry it out. It is probably true that physicians spend more time in evaluating a patient and establishing the direction of treatment than they do in explaining the various treatment procedures, yet the latter is certainly of equal importance. The physician should take the time to explain rheumatoid arthritis as a disease and describe its natural course. He must outline the objectives of the treatment to the patient and thoroughly explain the limitations of the various techniques. If this is done the patient is less likely to entertain hopes of cure or expect reversal of damage already inflicted

VOL 5 195

by the disease process. Somehow the physician must help the patient to gain insight into what can be accomplished by physical treatment. The patient must eventually realize that it requires an investment of time and effort on his part and any benefits will be the result of his own hard work.

The method of instruction should take into account individual differences in intelligence. Some patients will learn much more slowly than others; to some of these, the simplest procedures will appear too complicated to follow. Highly intelligent persons will grasp principles and techniques quickly, but since at best, only a certain amount of material can be retained from any one lesson, it is well to instruct the patient two or three times in the actual procedures he will be using at home.

The most successful method is demonstration by actual treatment. If possible, relatives or friends of the patient should watch the procedure and even take part in it, so that both the patient and whoever will be helping him are given the same view and the same understanding of the techniques of treatment. Clearly written instructions will serve to refresh the patient's memory when he is at home and "on his own."

Follow-up Care.—A highly important feature of the home-treatment program is the patient's regular re-evaluation by his physician, so that the treatment may be modified according to changes in the patient's condition. Frequent rechecks on an outpatient basis are necessary, and instruction in modified techniques or new techniques should be given as indicated. Adequate follow-up care may in some cases mean the difference between success and failure of the treatment; moreover, it may provide the key to the difficult problem of motivation of the patient in his long and arduous program of home care.

OL.
5
957

REFERENCES

1. Hill, D. F., and Holbrook, W. P.: Prevention and Treatment of Deformities in Rheumatoid Arthritis, J.A.M.A. **142**:718, 1950.
2. Treusch, J. V., and Krusen, F. H.: Physical Therapy Applied at Home for Arthritis: A Follow-Up Study With a Supplementary Summary of the Sedimentation Rate of Erythrocytes in 229 Cases of Arthritis, Arch. Int. Med. **72**:231, 1943.
3. Martin, G. M.: What Every Physician Should Know About Prescribing Physical Therapy, J.A.M.A. **142**:474, 1950.

REHABILITATION OF PATIENTS WITH RHEUMATOID ARTHRITIS

WILLIAM S. CLARK, M.D.,* HILDA B. CASE, M.D.,** AND
J. GEORGE FUREY, M.D.***

CLEVELAND, OHIO

From the Arthritis Clinic, University Hospitals, Cleveland, Ohio

(Received for publication Feb. 5, 1957.)

VOL
5
195

RHEUMATOID arthritis is an unpredictable disease which persists indefinitely, regardless of medical therapy, in the majority of individuals afflicted. From reported studies of its course, it can be estimated that over a period of years, only 15 per cent of affected patients may experience complete remissions of rheumatoid activity whereas over 50 per cent may continue to have stationary or progressive disease.[1]

Although patients with this disorder may have widespread lesions of vascular and connective tissue, rheumatoid in nature,[2] their principal handicaps evolve from inflammatory disease of the joints and accessory structures and consist of discomfort and locomotor disability. Functional capacity of the patient is impaired both by the manifestations of the chronic inflammatory process and the disturbances of joint mechanics accruing from deterioration of articular tissues. Constitutional manifestations, particularly asthenia, contribute significantly to the sum total of disability.

The prevalence of functional impairments among patients with rheumatoid arthritis is not known. A review of reports of therapeutic trials, appearing in the literature from 1951 to 1955, indicates a high degree of disability in those patients selected for the administration of new agents. Of 502 patients treated with adrenal steroids or phenylbutazone and classified by functional capacities, 43 per cent were limited to little or none of the duties of usual occupation or self-care and 21 per cent were bedridden or confined to a wheel chair.†

Whatever significance such statistics might have, it is apparent that therapy for rheumatoid arthritis should include, in addition to those agents which suppress symptoms, the application of other medical and nonmedical measures which can prevent, correct, or minimize physical handicaps with or without

Studies reported in this paper have been supported by the Cleveland Chapter of the Arthritis and Rheumatism Foundation.

*Associate Professor of Medicine, Western Reserve University.

**Assistant Professor of Physical Medicine and Rehabilitation, Western Reserve University.

***Instructor in Orthopedic Surgery, Western Reserve University.

†Data were compiled from reports in which the several authors applied criteria for functional status approved by the American Rheumatism Association.[3] These criteria, in brief, are: Class I, ability to carry on all usual duties without handicap; Class II, adequate for normal duties despite handicap of discomfort or limited motion in one or more joint; Class III, limited to only a few or no duties of usual occupation or self-care; Class IV, incapacitated, largely or wholly, with little or no self-care.

persistence or exacerbations of the basic inflammatory disease. That this can be achieved is indicated by observations concerning rehabilitation of the rheumatoid patient which have appeared in the literature in the past several years.[4-9]

DEFINITION OF REHABILITATION

Rusk considers rehabilitation to be a third phase of medicine which can be separated, at least conceptually, from diagnosis and medical or surgical treatment. It denotes a process whereby a patient is returned realistically to his greatest physical, mental, social, vocational, and economic usefulness, and, if employable, is provided an opportunity for gainful employment in a competitive industrial world.[10] Whitehouse defines rehabilitation as the process of mobilization of all available medical resources for whatever period of time is necessary to assist a patient in achieving a more useful and constructive life.[11] It is generally agreed that rehabilitation is an essential component of comprehensive medical care and is applicable alike to patients who may become employable and to those whose only realistic hope is a higher level of self-care.[12]

In a continuing or recurring disease such as rheumatoid arthritis, a concept of rehabilitation must emphasize the prevention of disability and maintenance of a reasonable level of performance over the lifespan as well as a return to a greater degree of independence of the patient already severely crippled.

PRINCIPLES OF REHABILITATION OF THE RHEUMATOID PATIENT

Standardization of a rehabilitation approach to rheumatoid arthritis is difficult because of the number of variables including the age, sex, general health, environment, and personal resources of the patient and the duration, severity, activity, distribution, stage, and therapeutic responsiveness of the disease. Criteria for classification of the stage, functional status, and therapeutic responsiveness have been recommended by a committee of the American Rheumatism Association.*[3] Such criteria are useful but do not adequately describe the patient or disease for rehabilitation purposes. For example, stage and functional status can be completely dissociated and the stage may not correlate with duration or severity. Moreover, much of the handicap may result from subjective phenomena which are not included in approved criteria.

Assuming that the disability is entirely due to arthritis, three categories for classification are useful, namely, disease activity, functional capacity, and role of the patient. Disease activity refers to the state of the inflammatory process as measured by clinical manifestations and laboratory tests. Functional capacity is indicative of physical performance including mobility, strength, coordination, and endurance. Role is a measure of dependence and characterizes the patient's adjustment in life as a sick or well person. In the final analysis, the major objective of rehabilitation is movement of the patient toward a well role.

*The Stage of the disease concerns the degree of presumable irreversible involvement rather than activity. Stage I is characterized by no bony change or subchondral bone atrophy; Stage II by cartilaginous and cortical destruction; Stage III by deformities such as ulnar deviation and subluxation, and Stage IV by fibrous or bony ankylosis.

There may be good or poor correlation among these three categories, and an analysis of the causes of dissociation is helpful for effective rehabilitation. Every physician experienced in rheumatoid arthritis knows at least one patient with severe disease and marked functional impairments who lives a normal life, working every day, to the amazement of everyone. This represents a substantial discrepancy between disease and role. A similar dissociation is represented by the patient with mild disease and adequate joint function who is extravagantly disabled. It is important to emphasize that the sick role may be necessary to the patient or required of the patient in the process of medical treatment, irrespective of potential performance or independence.

SPECIFIC OBJECTIVES

Because of the nature of the problem, significant rehabilitation objectives may only be achieved over long periods of time. No program for the rheumatoid patient can be considered adequate unless it is adapted to the years ahead. Likewise, no temporary gains for the patient are valid if they are to jeopardize the patient's health or dependence later. Realism in selecting short- and long-range goals is essential. More satisfactory long-range objectives can be achieved frequently by clearly defining intermediate goals and up-grading or down-grading the program in relation to changes in the patient, environment, or disease.

Specific objectives vary with the degree of disability. From functional Class IV to functional Class I, they include self-care in personal needs, mobility in bed or wheel chair, transfer activities (i.e., bed to chair, etc.), proficiency in activities of daily living, ambulation including stairs, automobile travel, use of public transportation, sheltered or competitive employment, social adequacy, and prevention of additional handicaps.

RESOURCES

The modern approach to medical rehabilitation emphasizes the application of specialized knowledge and techniques of many disciplines. The services of all medical specialties and of associated professional health personnel such as the nurse, social worker, physical therapist, occupational therapist, nutritionist, and vocational counselor may be applicable or indispensible.* The size of the community and the nature of its health institutions determine the availability of professional services, and, unfortunately, some geographical areas are less endowed than others. Specialized services are only effective when indicated, but when they are not available, rehabilitation can be difficult or impossible.

The problem of achieving purposeful collaboration among physicians and associated health professions concerned with total rehabilitation is not a simple one. A clear definition of patients' needs and goals is the first and most important step in achieving teamwork. The physician responsible for the patient must understand the objectives and how they are to be achieved. He must

*There will be no attempt to define, in this paper, the roles of individual specialties and of specialists in rehabilitation of rheumatoid patients.

also be able to enlist available health personnel for a broader, more accurate, and more detailed evaluation of the patient's problem and to mobilize resources which can assist the patient in achieving a well role. Personnel working with the patient must be able to communicate and share responsibility. Unfortunate products of specialism are the hazards of poor coordination of a comprehensive rehabilitation program over sustained periods of time and loss of focus on the patient. Such problems are just as significant to rehabilitation of patients with rheumatoid arthritis as hypercorticism and must be avoided by design.

Rehabilitation services beyond ordinary medical and surgical care are offered to some degree by general hospitals, chronic disease hospitals, rehabilitation institutes, and community agencies. Considering the wide variations in disease patterns, duration of the disease, and distribution in the population, it is unlikely that any single service organization can provide all needs for all patients. Furthermore, it is unrealistic to expect the average patient's problems to be resolved during a single hospital admission whatever its duration. Inpatient care should be carefully oriented to a home program for which the patient himself can assume maximal responsibility. Therapeutic measures which are arbitrary and which create unnecessary dependency on institutions must be applied with care.

VOL.
5
1957

Inpatient service is preferable for the initiation of a long-term rehabilitation program for patients in functional Class III or IV (ARA). Intermittent hospitalization, with each admission specifically designed for evaluation of progress and the achievement of stepwise objectives, can be extremely effective and economical. For the ambulatory patient, larger communities offer a variety of services which, if properly applied, can result in a rewarding rehabilitation program without institutional care. Such services include nursing, social case work, group work, physical therapy, occupational therapy, vocational testing and guidance, job retraining, placement, sheltered workshops, and special schools. It is unfortunate that many physicians are unfamiliar with available resources and/or fail to use them.

EVALUATION OF THE PATIENT

In practice, rehabilitation involves two processes. The first consists of the comprehensive evaluation of the individual, in medical, social, psychologic, and vocational aspects; the determination of rehabilitation goals which are feasible and desirable; and the development of a plan by which the individual can work toward the goals. The second part is the implementation of this program through medical treatment, physical therapy, vocational training, and other means. There is a necessary overlapping between these two parts because evaluation can be made properly only by continuing study during the course of the rehabilitation program.

The importance of complete and continuous study of the rheumatoid patient and the pathologic effects of the disease is self-evident. Investigations should include previous course, nature, and distribution of the inflammatory process, individual joint function, kinetics, posture, and compensatory mechanisms. Peripheral and trunk musculature should be carefully evaluated in

relation to mass, power, endurance, and coordination. Psychologic evaluation should include the patient's personality, intellectual capacities, aptitudes, interests, and reactions to the disease and to rehabilitation personnel. Knowledge of effectiveness in performing the simple and complicated tasks of daily living and vocational pursuits is a prerequisite for a rehabilitation program. Disabilities not due to rheumatoid arthritis should be given proper emphasis.

PROCEDURE

The importance of integration of rehabilitation measures with medical and surgical treatment has been demonstrated by Lowman.[9] Medical therapy for the disease is oriented toward two principal objectives, namely, amelioration of the clinical manifestations handicapping the patient and the establishment or maintenance of conditions most favorable to a natural remission of the disease. Therapeutic maneuvers aimed at a remission are empiric and consist of physical rest, amelioration of physiologic and psychologic stresses, and correction, if possible, of complicating diseases. Whereas there is general agreement on the value of such measures, there are no simple criteria to determine to what extent or degree or to what patients they should be applied, particularly when they seemingly conflict with total rehabilitation.

Rest.—To avoid therapeutic paradoxes, all specific methods of treatment should be evaluated in relation to long-range goals. A prudent physician may elect sanatorium-type treatment with emphasis on rest in patients with early disease or those patients with considerable rheumatoid activity or those who have experienced previous spontaneous remissions under similar conditions. The rest regimen is usually continued until a spontaneous remission is no longer a a realistic goal or until it becomes apparent that by pursuing such a program the patient may become firmly established in a sick role, rendering ultimate rehabilitation procedures ineffective. Compromising with the generally accepted value of physical rest is inherent in the rehabilitation approach. The removal of restrictions of physical activity should be related to long-range objectives and is indicated when it has been demonstrated that certain degrees of local or general rest are not necessary or may have ultimate adverse effects on performance. It should be emphasized that elected periods of physical rest can be as important in the rehabilitation approach as measures designed for the restoration of function. Less satisfactory compromises with necessary restrictions of physical activity are those forced by social and economic pressures or by inability of the patient to accept a regimen of rest. The fact that adrenal corticosteroids are so effective in abetting a denial of the long-range implications of rheumatoid arthritis may at times result in overemphasis on physical performance when the patient is, in fact, quite ill.

Drugs.—It is well established that the disabling clinical manifestations of rheumatoid disease can be suppressed to some degree by the systemic administration of salicylates, adrenal glucocorticoids, corticotropin, and phenylbutazone. Also, the joint manifestations may be altered favorably by the intra-articular administration of hydrocortisone or prednisone. There is wide but not universal agreement that gold salts administered parenterally have a similar sup-

pressive effect. The indications, contraindications, and hazards of these agents are discussed elsewhere in this issue. The use of narcotics is considered undesirable for sustained relief of discomfort.

The precise role played by this group of agents in rehabilitation is obvious in that some control of the disabling manifestations of rheumatoid disease is essential in most patients afflicted. The manner in which the measures are applied varies with the nature of the drug, condition of the patient, and objectives of therapy. Salicylates, preferably aspirin, in stable, maximal daily doses are indicated in all patients regardless of the degree of discomfort. The basis for this premise is the intrinsic safety of these compounds and the likelihood that stiffness which limits performance and disturbs coordination is present in almost all instances and is relieved in some degree by this means. The effectiveness of steroids in ameliorating stiffness, soreness, pain, aching, weakness, and fatigue has made rehabilitation, including vocational programs, realistic in a large number of patients who would remain dependent with other forms of therapy. A striking feature of steroid therapy is its favorable effect on the functional status of the patient. The anti-inflammatory properties of these compounds permit more effective physical and occupational therapy, reduce the hazard of functional retrogression due to exacerbations and give assurance that a certain level of physical activity and mobility can be sustained. It should be emphasized that a desirable functional level of a patient cannot be maintained if it is dependent on an intake of an adrenal steroid that will result in significant hypercorticism. Thus, dosage must be adjusted to the probable tolerance rather than the level of symptomatic improvement. Gold salts and phenylbutazone are useful in proportion to the degree that they suppress disabling manifestations and the length of time they can be administered.

Although stability of the medical regimen is highly desirable, it must be re-evaluated continually in relation to needs occurring during the process of total rehabilitation. For example, corrective exercises and orthopedic procedures may necessitate temporarily the use of narcotics or additional steroids. Also, a rehabilitation goal, in itself, may constitute the only reasonable indication for adrenal steroid therapy in some instances.

Physical Modalities.—The amelioration of articular symptoms by heat is generally accepted, although its effectiveness is not easily determined because of the subjective nature of the response. Complicated heating devices such as short-wave diathermy, infrared, ultrasound, whirlpool baths, Hubbard tubs, and paraffin baths have not been demonstrated to have specific therapeutic effects and probably have no advantages over the use of hot tubs or showers properly prescribed for daily use. Moreover, if applied indiscriminately, special modalities may nurture an undesired or uncontrolled dependence on personnel or the institution involved. Prescriptions for heat should be simple and although utilized during inpatient service, should be applied in a manner that can be sustained during home care (i.e., hot tub or shower baths).

Indispensable in the rehabilitation approach is the application of those measures which prevent, redevelop, or substitute for the impaired locomotor function of rheumatoid arthritis. Joints may be splinted or braced to alleviate

VOL.
5
1957

symptoms, prevent trauma, or provide strength and stability. Systematic active exercises are necessary to maintain muscle power and endurance and to prevent or correct insidious losses of function. Resistance exercises may be indicated to restore power to weakened muscle groups or develop compensatory musculature. Assistive and passive exercises may be necessary as conditioning measures for effective active exercising or to improve range of motion by stretching. Mechanical devices can be contrived to assist certain motions; repetitive active and assisted motions achieved by occupational devices have psychologic value and a favorable effect on coordination and endurance. Self-care, social, or vocational demands can be simulated in exercise programs for therapeutic efficiency. External supportive devices (i.e., walkers, crutches, canes) may be necessary on a temporary basis for protection of weight-bearing joints or for assistance to certain movements which are essential to restoration of adequate muscle performance. Such devices can be adapted to disabilities of the upper extremities. Compensatory self-help devices covering most activities of daily living are available for patients in whom functional return is delayed or improbable.*

Physiologic studies concerning specific responses to exercise therapy in the rheumatoid patient are singularly lacking. The effects of repetitive or stressful joint motion on the severity of synovial inflammation and bone and cartilage destruction are not known. Limited studies have indicated that the gross response to exercise of rheumatoid muscle tissue parallels that of normal response.[13]

Surgical Procedures.—Surgical amelioration of rheumatoid disability is most effective when related to specific rehabilitation goals rather than isolated joint function. There are no criteria to indicate when in the course of the disease surgical procedures are less hazardous or more likely to succeed. It is reasoned that arthroplasties performed during remissions of the inflammatory process are more likely to be successful. All surgical procedures can conceivably precipitate exacerbations. It has been our experience that this does not constitute a contraindication for orthopedic surgery essential to rehabilitation. The term "burned out" arthritis is probably a misnomer[14] and is of no significance in the surgical approach.

A large number of orthopedic procedures have been advocated for correction of arthritic deformities. It is frequently difficult to determine which operation is more desirable for a specific handicap. Certain procedures on Stage III and Stage IV residua have resulted in only minor improvements in the operated joint but have been of considerable benefit in reducing total disability.

Excision of the acromion process may relieve uncontrollable pain in the shoulder joint.[15] Although this procedure may result in only slight increase in glenohumeral motion, scapulothoracic motion may be markedly enhanced. In rare cases with severe disease of the glenohumeral joint, arthrodesis may be

*In our opinion, the most important single measure in the care of the rheumatoid patient is a properly designed exercise program for which the patient can assume major responsibility. Space does not permit detailed descriptions of exercises for specific disabilities. These are found in several textbooks. All patients in this clinic receive instructions in posture, gait, and active range of motion exercises. Special exercises are prescribed as indicated.

VOL 5 195

necessary to relieve pain and thus improve upper extremity function. Improvement of elbow function by surgical means has been moderately successful.[15] Radial head resection, alone, has proved beneficial in those cases where the major arthritic changes have occurred in the radiohumeral compartment. This procedure may result in substantial relief of pain, but the return of motion, except for pronation, may be disappointing. Arthroplasty of the elbow can be helpful in those patients with limited shoulder motion and elbow flexion to only 90°. Total joint resection is unnecessary since even the routine arthroplasty produces a moderate degree of relaxation, and instability of the elbow may be a source of concern if crutches are required.

Severe deformities of the wrist may require more than a molded leather gauntlet or cock-up splint, particularly if there is marked bone destruction and subluxation. In such instances, an arthrodesis may be helpful and a midposition between flexion and extension is thought to be the most advantageous position of fixation. This position enables the patient to get at objects within a short radius of the trunk with less rotation of the shoulder. Resection of the distal end of the ulna is performed in conjunction with wrist fusion to maintain or increase rotatory movement.

The most common effect of rheumatoid disease of the hand is the "intrinsic plus" deformity (flexion of metacarpophalangeal joints and extension of the proximal and distal joints).[16] Finger extensor tendons are displaced to the ulnar side of the metacarpophalangeal joint aggravating ulnar subluxation at these articulations. The short flexors and adductors of the thumb usually contract to produce flexion and adduction deformity at the metacarpophalangeal joint with secondary hyperextension of the distal joint. Space does not permit a review of operative planning for reconstruction of severely deformed hands.

Surgical procedures to the lower extremity may be necessary to restore weight-bearing and locomotion. Hip joint involvement, which is usually bilateral, poses a major problem. A flexion adduction contracture disturbs function of the opposite hip as well as all joints distally. Pain and loss of motion may be ameliorated by surgical reconstruction. The Smith-Peterson mold arthroplasty has proved over a longer period of time to give satisfactory results when patients are carefully selected, and the procedure is performed in the recommended manner.[17] Femoral head prostheses have been unpredictable and a few long-term follow-up studies have shown deterioration in a significant number rather than the progressive improvement frequently seen following the use of the mold. Arthrodesis of the hip should be avoided when there is multiple joint involvement. Hip denervation procedures are usually ineffective in the rehabilitation of the rheumatoid patient.

Fixed flexion contractures of the knees are common causes of rheumatoid disability and for satisfactory ambulation, extension to a minimum of 160° must be achieved. To accomplish this without significant residual discomfort is usually difficult. Hinged wedged casts can be effective in regaining extension and must be followed with bivalved casts for night use and, on occasion, light, long leg braces.[18] If a significant degree of motion in flexion is present, a supracondylar osteotomy might compensate for irreversible flexion contractures.

Posterior capsulotomy and lengthening of the hamstring tendons have been found ineffective. Arthroplasty of the knee, utilizing interposed fascia lata is occasionally attempted, but consistent satisfactory results are only rarely achieved. Arthrodesis of one knee can give a severely handicapped patient one stable and painless extremity for weight-bearing. Charnley's method of compression arthrodesis has simplified this procedure and usually results in solid union in 8 to 10 weeks.[19] The disability created by an ankylosed knee may be less than that resulting from instability and pain. Synovectomy of the knee joint in rheumatoid arthritis is rarely indicated since articular damage usually parallels the synovial change, and excision of only a minor portion of the lesion may have little benefit.

Rheumatoid changes in the foot contribute greatly to disability and may be quite amenable to surgical management. The increased laxity of these joints and contractures of the muscles can disrupt the normal mechanics of the foot to a marked degree. Splaying of the forefoot with associated hallux valgus deformity is frequently combined with severe hammer toes and large painful callouses under the metatarsal heads. Depression of the longitudinal arch is also commonly observed with more advanced changes in the tarsal joints. Many patients can be made quite comfortable with properly fitted shoes which would include a 2¼ to 3 inch heel for women, a reinforced medial counter, soft pliable leather top, and extra wide bunion last when necessary. Longitudinal and metatarsal pads should be included. In the more severe foot problems, custom-made molded arch supports of cork and sponge rubber may produce a greater measure of relief of foot pain providing the metatarsal and longitudinal pads are of correct height and if they are worn in large enough shoes.

The advanced deformities about the forefoot, as described above, may produce severe pain and disability for which a surgical approach is indicated. The Keller bunion operation is widely used for correction of the hallux valgus deformity. In addition, excision of the lateral four metatarsal heads is indicated if there are painful callouses underneath.[20] This procedure may not improve the gait significantly but does give dramatic relief of pain. Hammer-toe deformities can be easily corrected and the choice of procedures will depend on how many toes are involved and the associated deformities. Proximal phalangectomy may be performed alone or in conjunction with excision of the metatarsal head, or a resection arthrodesis of the proximal interphalangeal joint may be preferred.

Psychotherapy.—Psychotherapy in some form is an essential element of rehabilitation. Attempts have been made to describe patients who are unresponsive to rehabilitation measures and have shown among other characteristics, strong dependent tendencies.[21] There is not complete agreement on the nature or causation of the dependency pattern in rheumatoid disease. Ludwig has observed that some degree of regression to dependent or infantile attitudes is an accompaniment of every illness or injury and normally subsides with convalescence. Unresolved dependency conflicts, reactivated by the disease, can interfere seriously with treatment.[22] A substantial proportion of modern medicinal and physical therapy for rheumatoid arthritis encourages dependency of

the patient on physicians, therapists, and institutions. Such measures include hospitalization; injections of gold compounds; frequent examinations required during hormone therapy; periodic blood counts in the course of gold or phenylbutazone therapy; and physical treatment including diathermy, whirlpool, baking, and massage.

Awareness of the latter type of dependency is essential for an effective rehabilitation regimen. Although it is agreed that dependency on health resources is necessary, it can only be used therapeutically when completely understood and properly distributed and controlled. Restoration to an independent role must be gradual and in stages acceptable to the patient. The psychologic hazard of unrealistic objectives and promises should be carefully avoided.

There is no good evidence that rheumatoid disease or rheumatoid disability constitutes an a priori indication for psychiatric care, although in some instances, dynamic psychotherapy may be helpful or necessary. Rehabilitation personnel can and do play significant roles in the management of the psychologic aspects of the disease and disability. Relationships between the patient on one hand, and the social worker, nurse, physical therapist, occupational therapist, and vocational counselor on the other, are intrinsically therapeutic in that they may favorably alter dependency patterns, loss of self-esteem and self-confidence, environmental stresses, and difficulties in interpersonal relationships.

Vocational Rehabilitation.—As is demonstrated in another paper of this symposium ("Back to Work" Program), many rheumatoid patients perform effectively in competitive employment even with marked physical handicaps. The more severely afflicted patient may have difficulty using public transportation, be unable to sit or stand for sustained periods, or may lack efficiency and dexterity because of hand or upper extremity involvement. Those individuals with limited personal resources or disease patterns requiring selective employment may be benefited by vocational counseling. Vocational guidance includes evaluation of vocational and educational backgrounds and potential, and interpretation of findings and conclusions in relation to physical handicaps. The counselor is familiar with the job market, training facilities, working conditions, and sources of financial assistance and is trained to provide continuing psychologic support to the patient.

EVALUATION OF RESULTS

All of the well-known problems of evaluation of simple medical therapy in this disease are compounded by the large subjective component in the rehabilitation approach. Functional capacities can be measured, but determination of the results of individual services in a total effort is an overwhelming problem. Critical physicians can rightfully ask if some of the more dramatic results are not a result of chance or the extraordinary interest in the patient by the many people involved. Rehabilitation studies should emphasize evaluation of the effects of these various services.

SUMMARY

A survey of the rehabilitation approach to rheumatoid arthritis has been presented. The complexities of the disease and of the processes of integrating

therapeutic measures have been cited. The wide variety of measures and resources applicable to rehabilitation goals has been emphasized.

REFERENCES

1. Short, C. L., and Bauer, W.: The Course of Rheumatoid Arthritis in Patients Receiving Simple Medical and Orthopedic Measures, New England J. Med. **238**:142, 1948.
2. Bauer, W., and Clark, W. S.: The Systemic Manifestations of Rheumatoid Arthritis, Tr. A. Am. Physicians **61**:339, 1948.
3. Steinbrocker, O., Traeger, C. H., and Batterman, R. C.: Therapeutic Criteria in Rheumatoid Arthritis, J.A.M.A. **140**:659, 1949.
4. Dacso, M. M., and Rusk, H. A.: Rehabilitation of the Chronic Arthritides, Rheumatism **7**:6, 1951.
5. Newman, M. K., and Murphy, A.: Physical Medicine and Rehabilitation; Application to Chronic Arthritis, J. Michigan M. Soc. **50**:1031, 1951.
6. Gillmor, C. S.: Rehabilitation of the Rheumatoid Arthritic Patient, J. Missouri M. A. **49**:976, 1952.
7. Coss, J. A.: Symposium on Prolonged Illness; Medical Treatment and Rehabilitation Techniques in Rheumatoid Arthritis, M. Clin. North America **37**:815, 1953.
8. Ragan, C.: Keeping the Patient With Rheumatoid Arthritis Employable, Indust. Med. **22**:309, 1953.
9. Lowman, E. W.: Rehabilitation of the Patient With Chronic Rheumatoid Arthritis, J. CHRON. DIS. **1**:628, 1955.
10. Rusk, H. A., and Taylor, E. J.: New Hope for the Handicapped: The Rehabilitation of the Disabled From Bed to Job, New York, 1949, Harper & Brothers.
11. Whitehouse, F. A.: Teamwork: Clinical Practice in Rehabilitation, Exceptional Children **19**:143, 1953.
12. Report of Commission on Chronic Illness, Chronic Illness News Letter **6**:6, 1955, Baltimore, Maryland.
13. Clark, W. S., Watkins, A. L., Tonning, H. O., and Bauer, W.: The Effects of Resistance Exercises on the Nitrogen, Phosphorus, and Calcium Metabolism of Patients With Rheumatoid Arthritis, J. Clin. Invest. **33**:505, 1954.
14. Steiner, G., Freund, H. A., Leichtentritt, B., and Maun, M. E.: Lesions of Skeletal Muscles in Rheumatoid Arthritis; Nodular Polymyositis, Am. J. Path. **22**:103, 1946.
15. Smith-Peterson, M. N., Aufranc, O. E., and Larson, C. B.: Useful Surgical Procedures for Rheumatoid Arthritis Involving Joints of Upper Extremity, Arch. Surg. **46**:764, 1943.
16. Bunnell, S.: Surgery of the Rheumatic Hand, J. Bone & Joint Surg. **46**:764, 1955.
17. Aufranc, O. E.: Constructive Hip Surgery With Mould Arthroplasty, The American Academy of Orthopaedic Surgeons Instructional Course Lectures, **11**:163, 1954.
18. Rhinelander, J., and Ropes, M. W.: Adjustable Casts in the Treatment of Joint Deformities, J. Bone & Joint Surg. **27**:311, 1945.
19. Charnley, J.: Compression Arthrodesis, Including Dislocation as a Principle in Hip Surgery, Edinburgh, 1953, E. & S. Livingstone, Ltd., p. 92.
20. Rhinelander, J.: Personal communication.
21. Lowman, E. W., Miller, S., Lee, P. R., Stein, H., King, R., and Heald, L.: Psychosocial Factors in the Rehabilitation of the Chronic Rheumatoid Arthritic, Ann. Rheumat. Dis. **13**:312, 1954.
22. Ludwig, A. O.: Psychiatric Considerations in Rheumatoid Arthritis, M. Clin. North America **39**:447, 1955.

THE PLACE OF GOLD COMPOUNDS IN THE TREATMENT OF RHEUMATOID ARTHRITIS

R. H. FREYBERG, M.D.

NEW YORK, N. Y.

From the Hospital for Special Surgery and the Department of Internal Medicine, Cornell University Medical College

(Received for publication Feb. 5, 1957.)

VOL. 5 1957

IT IS desirable to appraise critically the usefulness, limitations, and troubles that may come from the use of a particular substance or class of compounds as therapeutic agents for any disease. Such a critical inventory of therapeutics is one of the important foundations on which progress in the practice of medicine depends. There is, however, no more difficult task in the science and art of medicine than to evaluate conscientiously the subject which is the title of this article, due to the following reasons: the etiology and pathogenesis of rheumatoid arthritis are unknown, indeed the exact nature of some of the pathologic and chemical features of this rheumatic disease is uncertain; the course of the illness is variable and unpredictable; the disorder is chronic and characterized by remissions and relapses affected by a variety of factors; there are many gold compounds which have quite different therapeutic behavior because of chemical and physical differences; many treatment schedules for these compounds have been employed; the manner in which gold compounds produce their effects is not known. One is faced therefore with the question, "What good is an agent about which little is known in the treatment of a disease about which so much is still unknown?" With full realization of the mysteries surrounding the problem, I undertake this challenging task.

In search for better treatment for this devastating rheumatic disease, hundreds of different agents have been tried for their therapeutic value on an empirical basis alone. In this circumstance gold therapy for rheumatoid arthritis had its advent about 30 years ago.[1] It had been demonstrated that various gold compounds, usually containing a sulfhydryl (SH) group, inhibited the growth of tubercle bacilli in vitro. Based on the thought that in at least some instances rheumatoid arthritis might be caused by tuberculous infection, these gold compounds were administered to patients with rheumatoid arthritis. From the earliest trials, reports of successes, failures, and toxic manifestations have appeared. Now, after many years of accumulated reports, there continue to be differences of opinion regarding the therapeutic value of gold compounds for rheumatoid arthritis. During the last decade, several summaries of reported clinical experiences have appeared which indicate a decided majority of favorable reports among a large series of patients.[2-6]

It has been difficult to blend reports from widely scattered investigators because of the differences in criteria of evaluation of benefits and toxicity and because of the lack of uniform criteria for judging therapeutic response in patients with rheumatoid arthritis. It is hoped that the criteria of Steinbrocker, Traeger, and Batterman[7] or those recently reported by Lansbury[8] will provide a more certain and sound basis for critical evaluation of the value of therapeutic agents. Until there has been time to apply these criteria, the evaluation of gold compounds for treatment of rheumatoid arthritis must be based upon the available experience of critical investigators and published reports of clinical trials.

I have presented evidence to indicate that gold compounds may help arrest the activity of rheumatoid arthritis,[4,9] as beneficial effects are believed to be due to this property of gold. However, the suppressive action of gold compounds on rheumatoid activity is not uniformly seen in all treated cases. The Tenth Rheumatism Review[6] referred to "more than 7,000 cases of rheumatoid arthritis treated with gold preparations" which "should have provided an impressive pool of information from which precise conclusions regarding the efficacy of chrysotherapy could be drawn. But certain common denominators essential for dependable comparisons and correlation of results are lacking, and despite such extensive experience the exact value of gold compounds has not been determined." The majority of investigators and critical clinicians consider gold therapy to have sufficient value to merit continued use. With the advent of corticosteroids in 1949, it was hoped that this hormone would be so superior therapeutically that it would not be necessary to employ gold compounds for treatment of rheumatoid arthritis. This hope has not been fully realized since steroid therapy also presents problems and has its limitations. Other forms of treatment still are to be considered and the wise selection of therapeutic agents is often an important problem in the management of patients with rheumatoid arthritis. It is appropriate, therefore, that "the place of gold compounds in treatment of rheumatoid arthritis" be reconsidered.

NATURE OF THERAPEUTIC EFFECT OF GOLD COMPOUNDS

When gold compounds are administered to patients with rheumatoid arthritis, there is little or no evidence of any effect for several weeks, after which time (if benefits result) there is gradual decrease in manifestations of the inflammatory process of the disease, usually the sedimentation rate decreases slowly and there is concurrent decrease in pain, stiffness, and limitation of motion. To these local joint improvements is later added improvement in general health. These improvements usually continue over succeeding months; the end point of improvement cannot be predicted. Some patients have a complete, or nearly complete, remission; the majority of those benefited have only partial remissions; some are not benefited. In comparison to the dramatic and rapid benefit from corticosteroid therapy, the improvement from gold therapy is slow indeed, but improvement may be long sustained even after therapy has been discontinued. This phenomenon is explained by the metabolism of gold, which is retained in the body in significant amounts for many months after its administration is discontinued.[10] Most important is the understanding that *all* of the benefit from gold

compounds used in the treatment of rheumatoid arthritis depends upon the suppressing effect this agent may produce on the rheumatoid (inflammatory) activity. Inactive rheumatoid disease and structural damage that has resulted from an active inflammatory process cannot be altered by a gold compound, nor can gold compounds straighten deformities, free ankylosed joints, or rebuild damaged cartilage or bone. Consequently the logical candidates for gold therapy are patients who have *active* rheumatoid arthritis with relatively little permanent articular damage.

The manner of action of gold compounds is not known. Recent studies suggest that gold salts exert their effects at the tissue level through some alteration in the cell metabolism; whether this is accomplished by alteration of enzyme activity, cell permeability or some other means is not known.

VOL.
5
1957

LIMITATIONS OF GOLD THERAPY

Anyone using gold compounds should be thoroughly familiar not only with what can and cannot be expected beneficially, but also with possible undesirable effects which may *lead* to "toxicity." It has already been stated that not all patients who receive gold salts will be benefited; that, when beneficial, the effects of gold come about only slowly, and that articular damages will not be repaired. Another important limitation is that the pathologic activity of this disease usually continues although oftentimes significantly suppressed, so that relapse or exacerbation of the disease usually will occur many months after cessation of treatment. Relapse has occurred in as many as 75 per cent of patients within 3 years of discontinuing treatment.[11] (To minimize this tendency to relapse, maintenance treatment, to be discussed below, has been devised.)

Another important limitation of this form of treatment is the likelihood of toxic reactions which attend the use of gold compounds. The manifestations of gold intolerance (toxicity) are numerous and varied. Most common are the cutaneous reactions which may be one of many sorts of dermatitis, usually pruritic. Stomatitis may accompany dermatitis or it may occur alone. Skin appendages may be damaged and alopecia may occur. Less common are nephritis and blood dyscrasias including thrombopenic purpura, hypoplastic anemia, and granulopenia; these may be serious and require prompt and proper treatment.

Physicians using gold therapy have been impressed with the fact that improvement in the arthritis usually accompanies manifestations of toxicity, especially dermatitis. This has been so universal that some investigators have suggested that suppression of rheumatoid activity depends upon the production of some form of gold toxicity. This seems untenable, however, for many instances of marked benefit, even complete remission of disease activity, have been observed unaccompanied by any manifestations of toxicity. Gold compounds may sometimes be reinstituted in smaller doses with resultant clinical benefit, and no recurrence of toxicity. It would seem advisable, therefore, that attempts should be made to benefit the patient by administration of gold compounds and to avoid toxicity whenever possible.

The mechanism of development of toxic manifestations has not been elucidated. Most likely gold toxicity in human beings is usually, if not always, a

hypersensitivity or allergic reaction to the gold-protein (globulin) complex in which form gold is known to circulate through the body.[12] Unfortunately, no method has been devised to predict whether or not a patient will tolerate a gold compound; cautious trial is the only dependable test of tolerance.

Prevention of Toxicity.—The employment of smaller doses of gold salts than were popular a decade or longer ago has resulted in fewer and less severe reactions.[12] Efforts to lessen toxicity have led to the development of insoluble gold compounds. Although toxicity following administration of such preparations has been less frequent, therapeutic response has been less satisfactory because the rate and amount of absorption of the insoluble compound is reduced and inconstant. Instances of dermatitis, stomatitis, and nephritis have been reported after the administration of insoluble gold compounds. Toxicity following administration of insoluble salts is likely to be protracted because adsorption and excretion are delayed. The use of insoluble compounds is not the solution to the problem of toxicity; the insoluble character of the preparation accounts for undependable and usually poor therapeutic effect.

Fear of toxicity from gold compounds need not be as great now as it was years ago, not only because greater knowledge concerning metabolism, transport, and excretion of gold has led to safer treatment schedules, but especially because dependable antidotes for the various forms of gold toxicity—corticotropin, corticosteroids, and British anti-lewisite are now available.

SELECTION OF PATIENTS TO BE TREATED WITH A GOLD COMPOUND

When contemplating use of gold compounds, or any other of the potent agents which suppress activity of rheumatoid arthritis, the clinician must face the question: "Are the potential benefits worth the risks entailed by this form of treatment?"

Under what circumstances is it appropriate to employ a gold compound for the treatment of rheumatoid arthritis? No hard and fast rules can be laid down to support the decision to institute gold therapy. The following considerations are recommended.

Benefit from gold compounds can be expected only when employed while the disease is active. The candidate for gold therapy is the patient with active synovial inflammation. If the disease can be arrested or its advance hindered before irreparable damage has occurred, crippling and incapacitation may be prevented. It is, therefore, in the early, active stage of the disease that gold therapy can be of greatest value. Adams and Cecil[3] found a larger number of complete remissions among patients treated during the first year or two of the disease, than in those treated in the late stages. It is a mistake to consider gold therapy "permissible" only as a last resort. If this is the basis for use of gold therapy, results will be unimpressive indeed, because the patient who suffers only from the crippling damage of inflammation which is no longer active cannot be rehabilitated by gold therapy; in such instances gold salts should not be used. In late stages of the disease gold therapy may check the progress of the illness only *if it is still active;* it can only prevent *further* damage to the joints; existing damage will not be reduced.

It is unwise to decide on any particular suppressive agent at the earliest contact with the patient who appears to have rheumatoid arthritis. Many times the diagnosis cannot be confidently made until disease has been carefully studied for several months. Of equal importance is the fact that many patients have such mild illness that, with a program of treatment which includes no suppressive agent, good to excellent results may occur. Under conservative treatment the activity of the illness may decline in the natural course of the disease. Hence, in early cases, it is reasonable to employ a good program of conservative treatment with careful evaluation of progress at monthly intervals; if the course is good, special agents need not be administered. If, however, the disease progresses relentlessly involving new joints, the patient becomes less comfortable and suffers progressively greater disability; and if it appears likely that irreparable articular damage will result, then it is proper to consider the addition of an agent that can have a significant suppressive effect on the rheumatoid process.

VOL.
5
1957

The only agents known to have a significant capacity to suppress rheumatoid activity are gold compounds and corticosteroids (or corticotropin). The choice is not easily made, for it is impossible to enumerate completely dependable criteria as a basis for selection. General guides, however, may be stated. It should be recalled that effects of gold salts come about much more slowly, often with less certainty and to a lesser degree than benefits from corticosteroids. On the other hand, these disadvantages are somewhat offset by: (1) longer sustained benefits from gold, and (2) the less disturbing character of the untoward effects that are likely to occur. Gold compounds do not produce hormonal effects, peptic ulcers, osteoporosis, or hypertension. It seems fair to consider corticosteroid the more potent agent both for therapeutic and for possible undesired effects.

One prototype, then, who is a logical candidate for gold therapy is the patient who has progressive disease, even though he receives good conservative therapy, but whose disease is not fulminating or "malignant." In these circumstances one can "gamble" on an agent which, though uncertain, may be very helpful and, in such a patient, the loss of the 3 to 6 months time necessary for trial will not jeopardize a potentially good result from another agent to be used later. In such a patient I often advise first a trial of a gold compound, especially if the patient is young, otherwise healthy, without a history of drug sensitivity, and whose disease is of short duration. When the patient is benefited, the results are usually gratifying. Should a good therapeutic effect fail to result over a period of 3 to 6 months, the physician may then employ corticosteroids. Should toxicity result from gold therapy, corticosteroid may be used with the satisfaction that dual benefits will result—control of the gold-induced toxicity, and suppression of the rheumatoid activity.

Other patients who are likely candidates for gold therapy are (1) those who have progressive disease even when receiving good basic treatment, and who have diabetes, severe hypertension, recent psychosis, or an active peptic ulcer, i.e., those in whom it would seem unwise to use corticosteroid as the suppressing agent; and (2) patients who develop a serious complication of steroid therapy (peptic ulcer, hypertension, diabetes, pathologic fracture, etc.) for which reason it is necessary to discontinue the steroid. That favorable results may occur under

these circumstances is graphically demonstrated in Fig. 1. Whenever gold therapy is considered, I believe it is extremely important to discuss the problems frankly with the patient. It is paramount that the patient realize both sides of the question—the possible toxicity as well as the desired salutary effects. Such a discussion should, of course, be candid and honest, but should not provoke

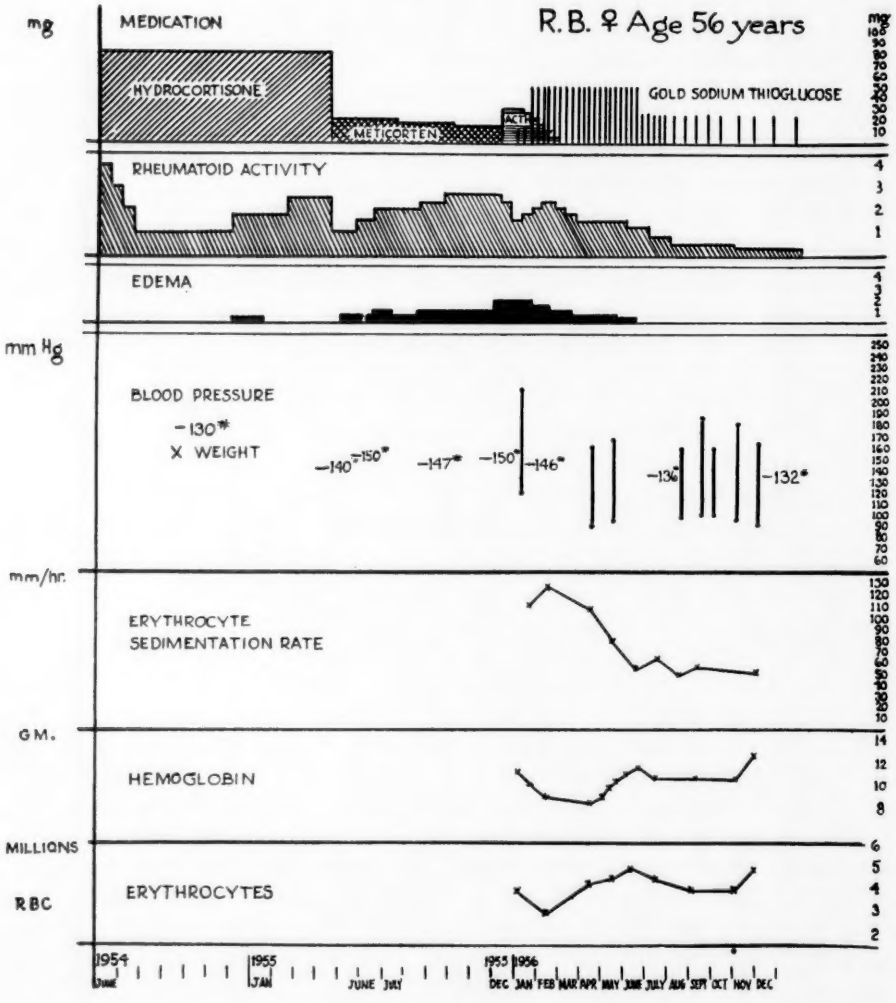

Fig. 1.—Graphic reproduction of changes in rheumatoid activity, edema, weight, blood pressure, erythrocyte sedimentation rate, hemoglobin, and erythrocytes during different forms of therapy in a middle-aged woman with rheumatoid arthritis.

fear. The patient should know *before* treatment is started that benefit cannot be promised and that toxic reactions may develop, rather than be surprised by one or both of these results.

For an adequate trial of treatment it is considered that at least 500 mg. of a compound containing approximately 50 per cent gold should be administered. The minimum time required for this (employing my own schedule of treatment) is 3 months.

CONTRAINDICATIONS TO USE OF GOLD COMPOUNDS

The most important contraindication to the use of gold salts is known previous toxicity from administration of gold or other heavy metals. Allergy to many other drugs should make one cautious in regard to use of gold compounds. Although experience has shown that some patients with multiple drug hypersensitivities may tolerate gold compounds and benefit from their use, it is considered wise to avoid the use of gold salts in such patients, and to select corticosteroid as the suppressive agent, since this therapeutic substance is known to have antiallergic properties. Similarly it is wise to avoid unnecessary treatment of any kind during pregnancy, so as to minimize chances of trouble both for the fetus and the mother. Fortunately, rheumatoid arthritis usually improves during pregnancy so that a suppressive agent seldom is needed, but if it is considered important to the welfare of the mother to give a gold compound (because of progressive incapacitating arthritis), experience in several patients has shown that there has been no undesirable effect on mother or baby.

Acute disseminated lupus erythematosus, diagnosed as rheumatoid arthritis, is often intensified when gold is administered. This disease is considered a contraindication to gold therapy. There are still unsettled problems in chronically ill patients who have clinically characteristic rheumatoid arthritis with a positive L.E. phenomenon. Many of these have received gold therapy with no evident trouble, but more study is needed in order to determine whether these patients have less tolerance for gold salts and whether such treatment should be withheld.

Previous liver or kidney disease does not contraindicate the use of gold compounds, but during seriously impaired function of these organs gold salts should not be used. The danger is not that toxicity is more likely to occur but that it would be poorly tolertaed when combined with the already existing illness. Similar considerations apply when a severe blood dyscrasia (anemia, purpura, etc.), uncontrolled diabetes, or cardiac failure exists. Such illnesses should be controlled or eliminated before gold compounds are used.

Chronic dermatitis, including psoriasis, does not contraindicate gold therapy. Usually the existing skin disorder is not adversely affected even though dermatitis may result from intolerance to the gold compound.

Debilitation from any cause should militate against the use of a gold compound. Age alone is not a contraindication to gold therapy if general health and nutrition are good.

METHOD OF TREATMENT

Selection of Gold Compound.—Many gold compounds are available. These include complex crystalline salts, soluble and insoluble, and colloidal suspensions of the element or of a simple salt. I and my collaborators[12,13] have shown that

injected colloidal suspensions are quickly taken up by the reticuloendothelial system and that dependable biologic effects cannot be expected from them. Also, insoluble gold salts injected intramuscularly show great variability of absorption, which is usually poor and always slow and incomplete. The preparations shown by metabolic studies and by clinical trial to be the most dependable and satisfactory for practical use are the soluble gold salts, such as gold sodium thioglucose, gold sodium thiomalate, and gold sodium thiosulfate. Of these, only the last can be given intravenously, but there is no advantage in using the intravenous route, unless it be to eliminate any chance of incomplete absorption from a muscle depot. In my experience the intramuscular route of administration has been found the most practical.

Schedule of Dosage.—The manner of treatment has varied considerably among different clinicians. I use one of the soluble gold salts containing 50 per cent gold, either gold sodium thioglucose or gold sodium thiomalate, and give weekly intragluteal injections containing the following dosage for adults of average size.

First injection	10 mg.
Second injection	25 mg.
Third through twenty or twenty-four injections	50 mg.

If no improvement results after this amount of treatment, the use of gold is considered to have no value and is discontinued. If improvement is observed, the same dose of the salt is given at 2-week intervals for 4 to 6 more injections, then at 3-week intervals for another 4 to 6 injections, and thereafter at monthly intervals as "maintenance treatment" for a year or longer until it is thought that the disease is suppressed and that further treatment will be of no value. Should exacerbation occur during maintenance therapy, weekly injections may produce more suppressive effect.

For children the treatment schedule is similar except that the dose in each injection is reduced in proportion to body size.

Many other treatment schedules have been employed. In Europe, many clinicians prefer larger weekly doses, and some advise more frequent injections. Some American physicians have reported good results from smaller doses than outlined in this paper. Considering the knowledge of metabolism of gold and based upon extensive trials, I believe the plan outlined is preferable for most patients.

It is important that strict precautions be taken to recognize early evidence of intolerance or toxicity. Should toxic manifestations develop—and they may appear at any time during the use of a gold compound—administration of the drug should be discontinued. After all signs of toxicity disappear, provided the disorders have been mild, smaller doses are sometimes tolerated and beneficial. Experience is the best guide in this circumstance and trial is the only way to determine whether more gold compound can be tolerated. It should not be employed after a severe form of toxicity. If treatment has been discontinued for any reason, and a gold compound is again used, a small initial dose and only small increases should be employed when it is recommended.

The prolonged, combined use of gold compounds and corticosteroids has been found to have no merit. Sometimes it is practical to use corticosteroids for 6 to 8 weeks at the beginning of gold therapy in severely painful and progressive disease until the effects of gold therapy begin.

PRECAUTIONS

Only those physicians who know the nature of the therapeutic and toxic potentialities of gold compounds should attempt to use them therapeutically. The physician should examine the patient before each injection for any symptoms or clinical signs of toxicity. It is helpful to inquire regarding pruritus, sore mouth, metallic taste, and irritation of eyelids which are among the early symptoms of toxicity. Inspection of the eyes, mouth, and skin, including that of the auditory canal, should be made. Laboratory studies should include urinalyses and erythrocyte and leukocyte blood cell counts done weekly until 500 mg. of a gold compound has been injected; thereafter, before each second injection. Additional laboratory studies may be indicated by symptoms or signs of toxicity (platelet count if purpura develops, etc.). Leukopenia, rapid decrease in hemoglobin, erythrocyte count, or platelets, the occurrence of albuminia, hematuria, pruritus, dermatitis, or stomatitis are danger signals; however, gold toxicity is not always the cause of these changes. A rapid reduction in erythrocyte sedimentation rate may forebode clinical manifestation of toxicity. Should any suggestion or definite sign of toxicity develop, use of the gold preparation should be discontinued. In case of doubt it is wise to consider it likely that intolerance to gold may be developing and to withhold further use of the compound until the picture is clarified.

TOXICITY

Toxicity from gold compounds depends upon several factors including the preparation employed, the manner of its administration, especially the size of dose at each injection, the precautions taken, and, of course, the criteria used to evaluate toxicity. All preparations of gold which possess potential therapeutic value also have potential toxicity. Toxicity can occur at any time during or shortly after treatment although usually it appears after 300 to 400 mg. of the gold compound has been injected (given according to the schedule described).

The many different manifestations of intolerance to gold have already been mentioned. The incidence of toxic complications is variously reported, as little as 4 per cent[14] and as high as 51 per cent.[15] The average incidence of toxic manifestations, including minor reactions, is 37 per cent calculated from reports by different authors. Some minor complications occurring during gold therapy may not be a manifestation of gold toxicity. This was clearly shown by Fraser,[16] who found that among a group of arthritis patients receiving injections of a placebo (to control results of clinical trials of gold compounds given to another group of patients), the physician, who did not know the injections were placebos, considered various complications to be manifestations of "gold toxicity" in 27 per cent of the patients! When smaller doses of gold salts are used, as in the schedule outlined herein, the incidence and severity of toxicity are significantly less than when larger doses, as initially popular, are employed.[12]

TREATMENT OF TOXICITY

When toxicity develops, use of the gold compound should be promptly discontinued. If the toxicity is mild it is wise not to employ measures that will cause rapid elimination of the gold because this compound concurrently has a beneficial effect on the rheumatic disease. If the toxicity is in the form of serious blood dyscrasia, vital organ disease, or dermatitis which causes much discomfort, antidotes should promptly be employed. The effectiveness of 2, 3-dimercaptopropanol (BAL) has been clearly demonstrated. This antidote is most effective when injected at 4-hour intervals for 4 to 6 injections daily for 2 days, and twice daily for the following 5 to 8 days. The dose used is the same for each injection and is calculated on the basis of body weight: 25 mg. (0.025 c.c. of the prepared solution) per kilogram of body weight.

Because of several undesirable features which usually accompany the use of BAL, cortisone derivatives or corticotropin, which are very dependable agents for the treatment of gold toxicity, have become the preferable antidotes. Corticotropin used in a slow intravenous drip, 25 units daily for several days, may suffice. For more prolonged treatment ACTH gel or zinc corticotropin, 40 or 50 mg. intramuscularly daily are very effective. In ambulatory patients, hydrocortisone 40 to 80 mg. orally daily, or prednisone or prednisolone 10 to 20 mg. daily usually control the reaction. Treatment should be employed so long as needed.

SUMMARY

Based upon current knowledge, it is concluded that although empirical, gold compounds may have a suppressive effect upon rheumatoid activity. Their usefulness is limited by uncertainty of therapeutic effect, slowness of action, and potential complications due to toxicity from the heavy metal. Recommendations for the selection of a gold compound for therapy, the schedule of administration, precautions during its use, and management of toxic reactions are presented.

Although its action is less dependable, slower, and less potent than that of corticosteroid as an antirheumatic agent, there are many circumstances when administration of a gold compound is practical, reasonable, and beneficial for the treatment of rheumatoid arthritis. These circumstances have been evaluated.

With increasing research into the nature of rheumatoid arthritis, it is to be expected that treatment will be improved. Until this happens, clinicians should employ the therapeutic agents available as wisely as possible. The physician who employs gold compounds for the treatment of rheumatoid arthritis should have a comprehensive understanding of this therapeutic agent and should recognize its limitations and potential hazards as well as its potential value.

REFERENCES

1. Lande, K.: Die günstige Beeinflussung schleichender Dauerinfekte durch Solganal, München. med. Wchnschr. **74**:1132, 1927.
2. Sundelin, F.: Complications Due to Gold Treatment in Chronic Polyarthritis, Nord. med. **37**:303, 1948.
3. Adams, C. H., and Cecil, R. L.: Gold Therapy in Early Rheumatoid Arthritis, Ann. Int. Med. **33**:163, 1950.
4. Freyberg, R. H.: Present Status of Gold Therapy for Rheumatoid Arthritis, J.A.M.A. **143**:418, 1950.

5. Waine, H., Baker, F., and Mettier, S. R.: Controlled Evaluation of Gold Therapy in Rheumatoid Arthritis, California Med. **66**:295, 1947.
6. Robinson, W. D., and others: Rheumatism and Arthritis Review, Ann. Int. Med. **39**:497, 1953.
7. Steinbrocker, O., Traeger, C. H., and Batterman, R. C.: Therapeutic Criteria in Rheumatoid Arthritis, J.A.M.A. **140**:659, 1949.
8. Lansbury, J.: Quantitations of the Activity of Rheumatoid Arthritis, Am. J. Med. Sc. **231**:616, 1956.
9. Freyberg, R. H.: In Comroe's Arthritis, Hollander and collaborators, ed. 5, Philadelphia, 1953, Lea & Febiger, p. 251.
10. Freyberg, R. H.: Gold Salts in the Treatment of Chronic Arthritis: Metabolic and Clinical Studies, Proc. Staff Meet. Mayo Clin. **17**:534, 1942.
11. Ragan, C., and Tyson, T. L.: Chrysotherapy in Rheumatoid Arthritis: Three-year Study of One Hundred and Forty-two Cases, Am. J. Med. **1**:252, 1946.
12. Freyberg, R. H., Block, W. D., and Wells, G. S.: Gold Therapy for Rheumatoid Arthritis. Considerations Based Upon Studies of the Metabolism of Gold, Clinics **1**:537, 1942.
13. Freyberg, R. H., Block, W. D., and Levey, S.: Metabolism, Toxicity and Manner of Action of Gold Compounds Used in the Treatment of Arthritis, J. Clin. Invest. **20**:401, 1941.
14. Oren, H.: Gold Salts in Treatment of Rheumatoid Arthritis: A Report of One Hundred and Fifty Additional Cases, M. Rec. **159**:420, 1946.
15. Graham, J. W., and Fletcher, A. A.: Gold Therapy in Rheumatoid Arthritis, Canad. M.A.J. **49**:483, 1943.
16. Fraser, T. N.: Gold Treatment in Rheumatoid Arthritis, Ann. Rheumat. Dis. **4**:71, 1945.

VOL.
5
1957

PHENYLBUTAZONE IN RHEUMATOID ARTHRITIS

CHARLEY J. SMYTH, M.D., AND GLENN M. CLARK, M.D.

DENVER, COLO.

From the Department of Medicine, University of Colorado School of Medicine

(Received for publication Feb. 5, 1957.)

VOL
5
195

THE evaluation of any new drug introduced for the treatment of patients with rheumatoid arthritis is a most difficult task. This becomes particularly evident in long-term studies in which an attempt is made to appraise the end results of a therapeutic agent. Many experienced observers who have given thoughtful consideration to this problem seriously doubt the reliability of the methods currently used in measuring the response of new agents in this disease. Data from three carefully conducted investigations at the universities of Harvard,[1] Columbia,[2] and Edinburgh[3] clearly indicate the need for great care in attributing changes to a given program of management in this notoriously variable disease. These controlled trials offer condemning evidence against the value of a variety of agents which have been widely used and favorably considered in numerous previous reports. The results after one year of the comparative study conducted by the British Empire Rheumatism Council,[4] which showed no significant difference between a group of patients treated with cortisone and a similar group treated with aspirin, are particularly revealing. The observed clinical improvement and radiologic evidence of joint deterioration occurring to a similar extent in both treated groups is surprising in view of the often dramatically favorable immediate results of hormone therapy. In view of these and other reports, the need for better methods for measuring the activity of this disease and for more objective and dependable studies in this field is obvious to all.

This current clinical investigation to determine the value of phenylbutazone (Butazolidin*) in rheumatoid arthritis was undertaken with full realization of the pitfalls in the existing methods, but with the hope of devising and applying some new control methods and perhaps of offering data which would be statistically valid. In addition, with the wide divergence of opinion regarding the relative toxicity of this drug, it was considered of interest to report an analysis of toxic reactions occurring in the above patients and also in 129 additional patients who received phenylbutazone for a variety of other rheumatic disorders.

These studies were supported in part by grants from the Boettcher Foundation, Denver, Colo., and Geigy Pharmaceuticals, Inc., New York, N. Y.

*Trade name of the Geigy Company, Inc., New York, N. Y.

METHOD OF STUDY

Observations were made in this study upon two groups of patients with rheumatoid arthritis. The first group was composed of 93 patients who received only phenylbutazone and were followed for periods varying from 3 months to 5 years. The second group consisted of 20 patients who were treated for a period of 11 months during which each patient received phenylbutazone, aspirin, and cortisone in sequence. The drugs were administered according to the "double blind" technique described below. The comparative effectiveness of phenylbutazone, cortisone, and aspirin in the suppression of inflammation was objectively measured in the smaller group.

GROUP I

Selection of Patients.—The patients which form the basis of this part of the report were chosen at random from among the indigent and part-pay patients attending the Arthritis Clinic of the Colorado General Hospital. In this group, the diagnosis was concurred in by two experienced clinicians and was based upon the usually accepted clinical and laboratory criteria. By the classification of the American Rheumatism Association, all patients were in Stage III or IV, and Class II, III, or IV. Many of these patients had previously received adrenocorticotropin, cortisone, hydrocortisone, or gold. With few exceptions, patients with cardiac failure, history of peptic ulcer, renal disease, or anemia were excluded from the study.

Of the 93 patients with rheumatoid arthritis in Group I, 64 were women and 29 were men. The mean age was 58 years, with the distribution by decades as shown in Table I.

TABLE I. AGE OF PATIENTS

Age in years	20	21-30	31-40	41-50	51-60	61-70	71-80	80
Number of patients	4	7	12	12	31	16	10	1
				(Mean age—58 years)				

One of the factors now recognized as a serious obstacle in judging the effectiveness of drug therapy in rheumatoid arthritis is the spontaneous fluctuation in the activity of the disease. There is a particularly high proportion of patients who improve during the first year of the disease irrespective of the type of therapy. Only four patients in this series had early disease (i.e., less than one year's duration). The duration of illness at the time when the drug was started in this group is indicated in Table II.

TABLE II. DURATION OF ILLNESS WHEN TREATMENT STARTED

Duration of illness	1-6 mo.	6 mo.-1 yr.	1-2 yr.	2-3 yr.	3-5 yr.	5-10 yr.	10-15 yr.	15 yr.
Number of patients	2	2	16	16	12	21	9	15

Treatment Schedule.—Phenylbutazone was given as oral tablets each containing 100 mg. of the drug. There was a wide range in the total daily dose (from 100 to 1,200 mg.). After the first few months of the study it became apparent that few patients tolerated the higher portions of the range, and daily dosage was accordingly reduced to 300 to 400 mg. per day.

Plan of Follow-up.—During the first month of therapy, each patient was seen at weekly intervals, and thereafter the interval between visits was never greater than one month. On each return visit the patient was questioned concerning any subjective improvement and the occurrence of gastrointestinal symptoms, pruritus, rash, swelling of the extremities, or other evidence of toxicity. The patient's weight, total white blood cell count, hemoglobin, and sedimentation rate were determined during each return examination. The functional capacity was evaluated. An attempt was made to measure the rate of structural change by serial roentgenograms of affected joints (usually hands or feet) taken at 6-month intervals.

VOL 5 195

GROUP II

Selection of Patients.—The 20 patients included in this group were selected by consecutive interview of patients with rheumatoid arthritis attending this clinic without regard to previous therapy.

The "Double-blind" Technique.—Two drugs, phenylbutazone and cortisone, were administered to each patient as identical tablets. Although the size was the same, the phenylbutazone tablets contained either 50 mg. or 100 mg. while the cortisone tablets contained either 12.5 mg. or 25 mg. One of the drugs was given for a period of 5 months, followed by a one-month period on identical tablets containing only aspirin (0.3 Gm.). Following this the opposite drug was administered for a period of 5 months. The order of administration of the test drugs was randomized and the nature and dosage of the tablets were unknown to both the patient and the physician. The number of tablets prescribed per day was governed by the subjective response of the patient, although in some cases the number of pills was restricted because of the appearance of signs of toxicity.

Plan of Follow-up.—On initiation of therapy and after each 5-month treatment period or one-month period of aspirin therapy, objective measurements of joint inflammation were made by the method described below. The erythrocyte sedimentation rates were determined at the same time and the functional capacity was estimated. By applying a modification of the measurement of joint surface reported by Lansbury and Haut[5] to a quantitation of the extent of inflammation in each joint, a "total index of inflammation" was calculated.

INDEX OF INFLAMMATION

Measurement of Degree of Inflammation.—Before and after each treatment period, all joints were systematically evaluated in terms of the classical signs of inflammation. The following criteria were used in this objective evaluation.

Heat and redness: Heat and redness were evaluated by palpation and inspection, respectively. No effort was made to quantitate these signs of inflammation; a "plus" (+) being recorded if either sign was present without equivocation.

The small joints of the hand were graded by recording one plus sign (+) or two plus signs (++) depending on whether the heat or redness involved one joint or more than one joint in each extremity. No effort was made to detect heat or redness in the shoulder or hip joints.

Swelling: Swelling in the proximal interphalangeal joints was measured after each treatment period by taking the total ring-size at the widest extent of the joints, using commercial jeweler's "size" rings. The base line was considered to be the smallest "total ring size" ever recorded. Changes from 10 to 20 per cent were arbitrarily assigned a one plus (+) value and greater changes were given a two plus (++) value. In those joints in which the presence of fluid was easily demonstrated (wrist, elbow, foot, ankle, knee, and metacarpophalangeal joints) a one plus (+) was recorded under each joint in which fluid was observed. The total circumference of the wrists and knees was measured with a steel tape and a one plus (+) represented an increase in total circumference of 10 per cent above the "base line."

OL.
5
957

Tenderness: Tenderness was recorded in two degrees; that demonstrated only on moderate pressure being given a one plus (+) value, and that elicited on gentle palpation a two plus (++) value. No effort was made to demonstrate tenderness in the hip joint.

Since inflammation is not easily demonstrated in the hips and shoulders by the classical signs, pain on motion of either moderate and severe degree was used as the criterion of inflammatory involvement of these joints, and was assigned a one plus (+) or two plus (++) value, respectively.

The degree of inflammatory activity under each of the above categories (heat and redness, tenderness, and swelling) was recorded as plus symbols as shown in Table III. This table shows the maximum number of elements of inflammation which may be recorded under this system.

Measurement of total joint inflammation: In an effort to express the total amount of joint inflammation, each plus (+) value was given a numerical value in terms of both the extent of inflammation and the per cent of total body joint surface involved. For example, in the proximal interphalangeal joints of both hands there is a total of 14 plus (+) marks which express the total possible extent of inflammation in these joints that represent 2.8 per cent of the total body joint surface according to the measurements of Lansbury and Haut.[5]

Therefore, as shown in Table IV each plus (+) recorded in the hands may be assigned a numerical value of 1/14 of 2.8 or an index of 0.2. The calculation and summation of all recorded plus values gives a total index of inflammation as a numerical expression. An index of 100 would express maximum degree of inflammation of total movable joint surface. The numerical values for each joint are shown in Table IV.

RESULTS OF THERAPY

Anyone who has seriously attempted to grade the results of therapy in rheumatoid arthritis recognizes that there are symptomatic responses which are so elusive and personal that they cannot be evaluated on a statistical basis. Unfortunately these are the very factors about which the patients are most concerned—pain, muscle spasm, weakness, anorexia, fatigue, and a lack of a sense

TABLE III. DISTRIBUTION OF POSSIBLE PLUS VALUES REPRESENTING POSSIBLE INCREMENTS OF INFLAMMATION

AREA INVOLVED		SIDE INVOLVED	HEAT	REDNESS	SWELLING		TENDERNESS	PAIN ON MOTION
					INCREASED CIRCUM-FERENCE	FLUID		
Hand	Proximal interphalangeal joints	Rt. Lt.	++ ++	++ ++	++		++ ++	
Hand	Metacarpophalangeal joints (including transverse intercarpals)	Rt. Lt.	++ ++	++ ++		++ ++	++ ++	
Wrist (including carpometacarpals)		Rt. Lt.	+ +	+ +	+	+ +	++ ++	
Elbow		Rt. Lt.	+ +	+ +		+ +	++ ++	
Shoulder (including acromioclavicular)		Rt. Lt.					++ ++	++ ++
Temporomandibular		Rt. Lt.					++ ++	
Feet	Proximal interphalangeal Metatarsophalangeal Transverse metatarsal	Rt. Lt.	++ ++	++ ++		+ +	++ ++	
Ankle (including talonavicular and talocalcanean)		Rt. Lt.	+ +	+ +		+ +	++ ++	
Knee		Rt. Lt.	+ +	+ +	+	+ +	++ ++	
Hip		Rt. Lt.						++ ++

of general well-being. In this analysis of the end results of phenylbutazone therapy, no attempt has been made to appraise subjective response.

TABLE IV

AREA INVOLVED		NUMBER OF MEASURABLE ELEMENTS OF JOINT INFLAMMATION (TABLE III)	APPROXIMATE PERCENTAGE OF TOTAL JOINT ARTICULATING SURFACE*	RATIO OF PER CENT TOTAL JOINT SURFACE TO NUMBER OF ELEMENTS OF INFLAMMATION	NUMERICAL VALUE OF EACH PLUS
Hand	Proximal Interphalangeal joints	14	2.8	$\frac{2.8}{14}$	0.20
Hand	Metacarpophalangeal joints	16	8.0	$\frac{8.0}{16.0}$	0.50
Wrist (including carpometacarpals)		11	10.0	$\frac{10.0}{11.0}$	0.90
Elbow		10	10.5	$\frac{10.5}{10.0}$	1.05
Shoulder (including acromioclavicular)		8	10.0	$\frac{10}{8}$	1.25
Temporomandibular		4	0.8	$\frac{0.8}{4}$	0.20
Feet	Proximal interphalangeals Metatarsointerphalangeals Transverse metatarsals	14	10.0	$\frac{10.0}{14.0}$	0.70
Ankle (including talonavicular and talocalcanean)		10	12.0	$\frac{12.0}{10.0}$	1.20
Knee		11	20.0	$\frac{20.0}{11.0}$	1.82
Hip		4	16.0	$\frac{16}{4}$	4.00

*Original joint surface areas were taken from the paper of Lansbury and Haut. Am. J. M. Sc. 232:150, 1956.

Attention has been concentrated upon three selected factors which may be measured with considerable degree of accuracy. These factors are: (1) suppression of the objective signs of inflammation; (2) changes in the functional capacity as manifested by the patient's ability to perform the tasks of daily living; and (3) structural changes as shown in serial roentgenograms of affected joints.

ANTI-INFLAMMATORY RESPONSE

Repeated objective measurements of the degree and extent of inflammation were made only on the 20 patients engaging in the comparative drug study. The numerical indices calculated from measurements of joints after periods of treatment with each drug are shown in Table V.

TABLE V. INDICES OF INFLAMMATION AND ERYTHROCYTE SEDIMENTATION RATES IN 20 PATIENTS WITH RHEUMATOID ARTHRITIS AS INFLUENCED BY PHENYLBUTAZONE, CORTISONE, AND ASPIRIN
(Values taken on last day of therapy with each drug)

PATIENT	INFLAMMATORY INDICES				ERYTHROCYTE SEDIMENTATION RATES*			
	INITIAL DATA	AFTER CORTISONE THERAPY (5 MO.)	AFTER ASPIRIN THERAPY (1 MO.)	AFTER PHENYL-BUTAZONE THERAPY (5 MO.)	INITIAL DATA	AFTER CORTISONE THERAPY (5 MO.)	AFTER ASPIRIN THERAPY (1 MO.)	AFTER PHENYL-BUTAZONE THERAPY (5 MO.)
O. B.	11.10	8.33†	7.66	3.84	50	20	45	45
L. C.	10.40	6.50†	15.00	1.80	50	32	48	42
N. C.	15.73	17.21	29.08	5.10†	40	43	46	36
I. D.	17.05	3.00	5.00	1.80†	48	40	44	48
D. E.	14.76	3.72	9.26	4.42†	45	38	30	21
M. G.	8.52	5.40	1.00	0.20†	34	25	30	38
L. Ho.	19.81	4.74†	17.48	28.18‡	28	28	—	38
M. H.	15.76	12.56†	12.60	11.50	46	48	—	38
L. Ha.	12.24	4.14†	24.05	15.96	47	42	45	38
Mg. J.	6.60	2.70	0.23	1.95†	48	41	45	44
Mr. J.	19.56	11.11	19.34	15.94†	11	44	47	—
M. L.	17.28	11.56	17.78	10.13†	43	6	40	40
M. M.	7.46	8.18	10.61	10.64†	41	34	34	44
C. M.	15.85	8.69	11.36	11.19†	23	14	18	12
J. M.	1.40	0.00†	6.04	0.00	40	28	28	45
Ce. M.	11.02	9.18	6.16	3.33†	30	14	18	18
L. N.	20.20	18.13	23.74	19.00†‡	36	44	35	40
E. O.	21.40	3.92†	15.65	17.18	—	40	46	15
V. P.	24.33	4.67	13.88	10.27†	31	37	38	36
M. V.	9.14	2.92†	11.38	10.13	43	40	32	31

*One hour (Wintrobe).
†First drug in series.
‡Failed to complete 5 months on phenylbutazone.

In our as yet limited experience, an index of inflammation of 12 or below is reasonably accepted by the patient and is usually associated with a functional capacity of 1 or 2. At the initiation of the study, 12 of the 20 patients had indices of 12 or higher. After treatment with cortisone for 5 months, only 3 patients had unsatisfactory indices and, after phenylbutazone, 5 patients. After the aspirin control period, 9 of the patients again showed levels above 12. That the order of administration of the drugs did not markedly influence the comparison is shown by the fact that the unsatisfactory indices with cortisone and phenylbutazone are nearly equally divided between the first and last treatment periods.

The mean indices for all 20 patients after treatment with each drug were aspirin, 12.856; cortisone, 7.333; and phenylbutazone, 9.128. Analysis of the initial indices shows that chance distribution gave a significantly higher mean

initial index in those patients starting phenylbutzone treatment periods (14.411) than that for cortisone treatment periods (12.435). Fig. 1 shows a graphic comparison of the change in mean inflammatory index during treatment with each drug. Statistical analysis shows that both phenylbutazone ($p = < .01$) and cortisone ($p = < .001$) suppressed the index after 5-month treatment periods, whereas during one-month treatment periods with aspirin placed between the other 2 drugs, the inflammatory index rose ($p = < .001$).

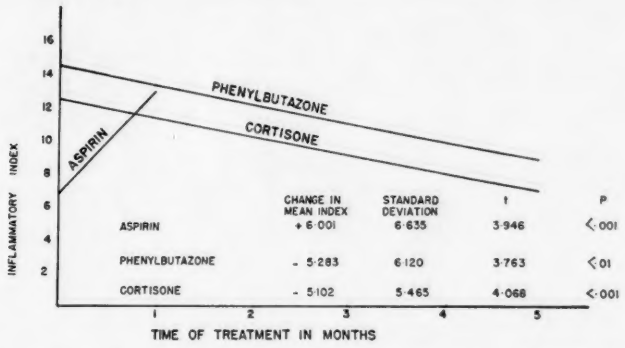

Fig. 1.—Mean inflammatory indices at initiation and termination of treatment with aspirin, phenylbutazone, and cortisone (20 patients).

Comparison of the effects of phenylbutazone and of cortisone is more difficult since the changes are similar. The mean dosage of phenylbutazone required to maintain the 18 patients who accepted treatment for the complete 5-month period was 360 mg. per day. The 2 patients who demanded a change in therapy while using phenylbutazone had received 800 mg. per day for satisfactory relief. (The comparable mean dosage with cortisone was 78.75 mg. per day. However, the 4 patients showing satisfactory indices on cortisone and not on phenylbutazone required at least 100 mg. per day for satisfactory relief.) Examination of more patients is needed before a final conclusion is reached, but these initial observations indicate that cortisone is more effective than phenylbutazone in suppression of inflammation, but usually requires relatively high (and probably toxic) dosage to produce the increased benefit.

The sedimentation rates taken at the time of each clinical measurement of inflammation are shown in Table V. Although the values obtained following cortisone therapy are somewhat lower than those obtained with aspirin or phenylbutazone, the differences are small, and do not reflect the marked changes noted on comparison of the inflammatory indices.

FUNCTIONAL CAPACITY, GROUP I

Since no data are available for the direct comparison of the effect of phenylbutazone on functional capacity over long periods of time, we were left in examination of the larger group of patients with the unsatisfactory alternative of accepting the ability of the patient to perform daily tasks at the initiation of therapy as a control level, and to observe changes in this level during the course of therapy with phenylbutazone.

VOL.
5
1957

Seventy-five patients (80.1 per cent) of those in Group I originally started on therapy reported initial improvement in at least a minimal degree in functional capacity. However, as the psychic effect of taking a new drug began to wear off, toxic effects became apparent, and as newer drugs became available, the number of patients remaining satisfied with phenylbutazone therapy began to fall.

Of the 93 patients started on therapy to date, 25 have taken the drug for periods varying from 1 to 5 years. Table VI shows the current status of the total group of patients and the reason for discontinuing phenylbutazone in those patients no longer taking the drug.

Examination of the data obtained from the 49 patients observed for longer periods of time (2 to 5 years), indicates that 19 patients have found phenylbutazone to be a satisfactory long-term therapeutic agent by these criteria.

TABLE VI. FOLLOW-UP STATUS OF 93 PATIENTS (GROUP I) WITH RHEUMATOID ARTHRITIS

STATUS	TOTAL SERIES (93 PATIENTS)	2 TO 5 YEAR FOLLOW-UP (49 PATIENTS)
1. Minimal activity or remission	11	8
2. On phenylbutazone with satisfactory control (Class II or better)	14	11
3. Discontinued for poor therapeutic response	18	14
4. Discontinued for toxicity	9	5
5. Discontinued because of patient's preference for another drug	13	3
6. Arbitrary transfer to another drug study	20	3
7. Left clinic (no record)	8	5

FUNCTIONAL CAPACITY, GROUP II

A comparison of the functional capacity on aspirin therapy alone with that while taking phenylbutazone and cortisone was made in the 20 patients studied by the "double-blind" technique. Table VII shows that of the 20 patients evaluated, 10 were unable to maintain satisfactory functional capacity (Class I or II) while taking aspirin, while only 3 patients were found to be in Class III on phenylbutazone therapy and one patient on cortisone therapy.

It is apparent that at least during the period of time during which these patients were studied that phenylbutazone and cortisone are both superior to aspirin as judged by maintenance of the functional capacity of patients taking the drugs in sequence on a double-blind study.

STRUCTURAL CHANGES

One of the aims of therapy is to reduce the degree of joint inflammation. It might appear logical to assume that the degree to which the inflammation is suppressed governs the extent of subsequent joint damage resulting from granulation tissue repair. However, in spite of the fact that symptoms of inflammation may be controlled and functional capacity maintained in rheumatoid arthritis by several types of drug therapy, there is no conclusive evidence to our knowledge that the structural changes characteristic of the disease are influenced by any therapeutic agent. In the past 5 years, roentgenograms have been obtained at 6-month intervals on a representative group of 40 patients with rheumatoid

arthritis, some of whom received steroids and others phenylbutazone. Roentgenograms of the small joints of the hands, wrists, and feet have proved to be the most valuable for the detection of progressive involvement of cartilage and bone. We have obtained no evidence that either type of therapy halts the progressive joint destruction of rheumatoid arthritis. Although most of the serial films show slight but unequivocal changes in patients with active rheumatoid arthritis, we have not as yet obtained sufficient data to make a comparison of the rate of destruction under therapy with various drugs. However, the fact that extensive changes may occur in the presence of satisfactory control of clinical symptoms with phenylbutazone is illustrated in Fig. 2 and 3, showing joint changes in patients followed for 23 and 40 months, respectively.

TABLE VII. CHANGES IN FUNCTIONAL CAPACITY IN 20 PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH PHENYLBUTAZONE, CORTISONE, AND ASPIRIN THERAPY

Figures represent "Class" by American Rheumatism Association criteria* at completion of treatment period.

PATIENT	INITIAL CLASS	CLASS AFTER CORTISONE (5 MONTHS)	CLASS AFTER ASPIRIN (1 MONTH)	CLASS AFTER PHENYLBUTAZONE (5 MONTHS)
O. B.	III	II†	IV	II
L. C.	II	II†	III	II
N. C.	III	II	III	II†
I. D.	III	II	III	II†
D. E.	I	I	II	I†
M. G.	III	II	I	II†
L. Ho.	III	II†	IV	III
M. H.	III	II†	II	II
L. Ha.	III	III†	III	II
Mg. J.	II	II	II	II†
Mr. J.	III	II	III	III†
M. L.	II	I	II	II†
M. M.	II	II	III	II†
C. M.	III	I	I	I†
J. M.	II	I†	I	I
Ce. M.	III	I	II	II
L. N.	II	II	III	III†
E. O.	II	I†	I	I
V. P.	III	I	III	II†
M. V.	II	I†	II	II

*Steinbrocker, O., Traeger, C. H., and Batterman, R. C.: J.A.M.A. 140:659, 1949.
†First drug.

CASE 1.—Patient C. D., a 62-year-old man, first suffered from generalized rheumatoid arthritis in 1950 and has been under continuous observation and treatment since that time. Oral phenylbutazone therapy was started in April, 1952, with a daily dose of 600 mg., and he remained on this amount of the drug except for a few days until January, 1955. During this period of 2 years and 9 months of continuous phenylbutazone administration, the daily dose was 600 mg. with the exception of two periods of 4 weeks each when he took 400 mg. per day. From the standpoint of the joint symptoms, he obtained moderate relief while taking the drug and was able to remain active at his work as an automobile parts salesman.

CASE 2.—Patient L. T., a 47-year-old patient with rheumatoid arthritis and advanced pulmonary emphysema, was maintained continuously on phenylbutazone from April, 1952, through June, 1956. The daily dose varied from 300 to 600 mg. with the latter amount being given for three of this 4-year period of uninterrupted therapy. While being maintained on this drug he was kept moderately comfortable, but over this period the disease remained active and progressive joint deformities with the characteristic ulnar deviation of the fingers developed.

VOL.
5
1957

Although fairly satisfactory symptomatic control of joint complaints was accomplished in each of these two cases, the natural course of the pathologic process of rheumatoid arthritis as reflected in the joint destruction shown on the roentgenograms was not arrested.

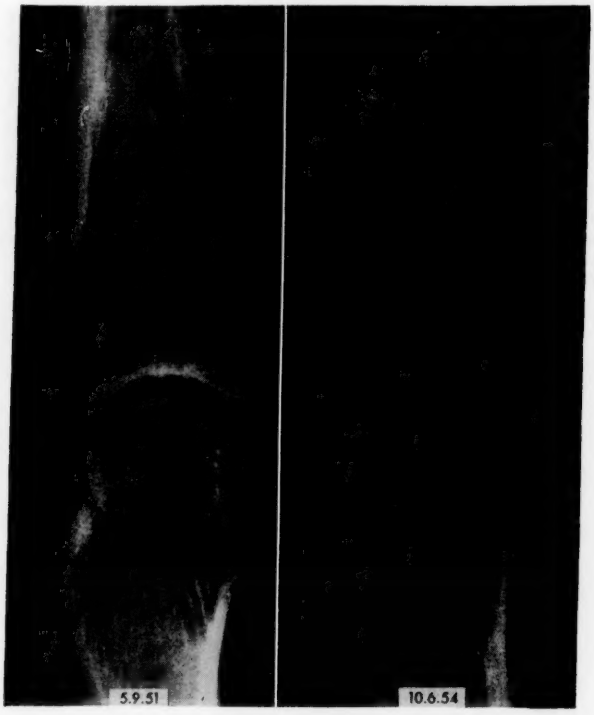

Fig. 2.—Case 1. Right second metacarpophalangeal joint showing complete loss of cartilaginous space with bone erosion during continuous phenylbutazone therapy.

TOXICITY ASSOCIATED WITH PHENYLBUTAZONE THERAPY

Since the initiation of this study, 222 patients have been treated with phenylbutazone for a variety of diseases including Group I of the patients with rheumatoid arthritis reported above. The diagnosis and length of treatment of the group of patients from which the toxicity data were compiled are shown in Tables VIII and IX.

In the total group, toxic reactions were encountered in 97 patients (43.8 per cent) and required discontinuing the drug in 30 patients (13.5 per cent). Of the 82 patients treated for longer than 6 months, 5 patients (6 per cent) developed toxicity, in each case a peptic ulcer. The distribution of the types of toxicity seen is charted in Table X.

One hundred and sixty patients received phenylbutazone in the range now generally used (100 to 400 mg. per day) and as shown in Table XI, the toxic reactions were less frequent, althought two developed fresh peptic ulcers.

Gastrointestinal Reactions.—Epigastric distress, nausea, and vomiting were frequently seen; 47 (21 per cent) of the patients complained of dyspepsia at some time during the course of therapy. Of these, 26 patients reported only mild nausea and 21 patients complained of severe gastrointestinal symptoms. It is of interest that 16 of the patients complaining of severe gastrointestinal symptoms were receiving doses of more than 400 mg. per day. Of these patients, 12 showed no toxicity on a smaller dose, 4 were unable to take a smaller dose, and 5 patients discontinued the drug because of dyspepsia. Later in the study, phenylbutazone was given only with meals, and in dosage of 400 mg. per day or less. By following this regime and using antacids as needed, significant dyspepsia was avoided in most cases.

VOL.
5
1957

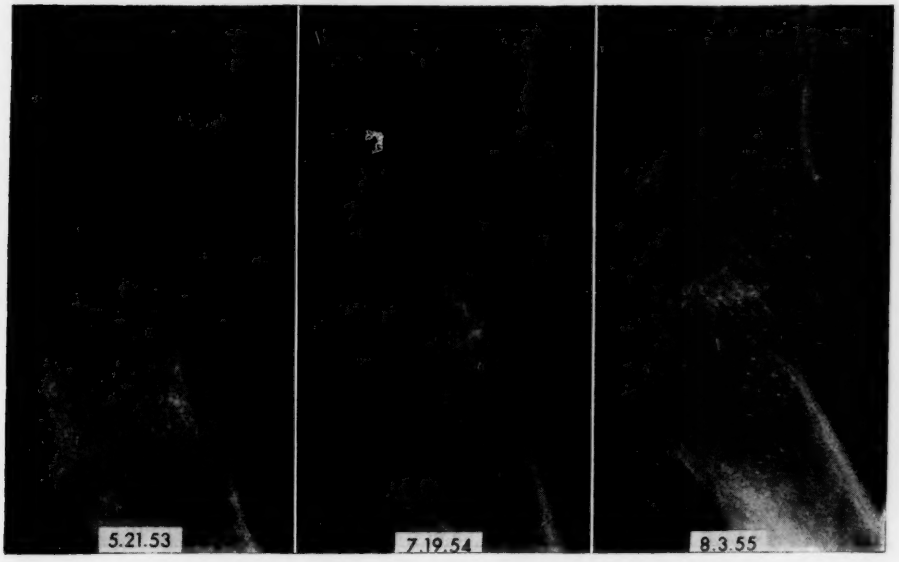

Fig. 3.—Case 2. Left fifth metacarpophalangeal joint showing progressive joint distruction, bone erosions, cystic changes and subluxation during uninterrupted phenylbutazone therapy.

Peptic Ulcer.—The most serious complication encountered was the occurrence or reactivation of peptic ulcers. Four deaths from complications of peptic ulcer have been reported by others[6-9] in patients taking phenylbutazone. Thirteen patients in the present series were shown to have ulcers on x-ray after the dosage and length of therapy shown in Table XII.

Seven of the patients denied any previous ulcer symptoms. In 6 cases, a careful history suggested ulcer activity at some time prior to the institution of therapy. Examination of the dosage and length of therapy indicates that ulcers may occur on small dosage after many months of treatment without previous complication. In three of the patients, gastrointestinal bleeding was the first manifestation of the presence of the ulcer. In all except 4 cases the drug was discontinued. The ulcer responded rapidly to conservative management in all

TABLE VIII

DIAGNOSES	NUMBER OF PATIENTS
Rheumatoid arthritis	93
Rheumatoid spondylitis	14
Osteoarthritis	88
Gout	18
Miscellaneous rheumatic diseases	9
Total	222

TABLE IX. LENGTH OF THERAPY

Length of therapy	1 mo.	1-6 mo.	6 mo.-1 yr.	1-2 yr.	2-3 yr.	3-5 yr.
Number of patients	43	97	32	30	8	12

TABLE X

TYPE OF REACTION	TOXICITY IN 222 PATIENTS RECEIVING PHENYLBUTAZONE		TOXICITY REQUIRING WITHDRAWAL OF PHENYLBUTAZONE	
	NUMBER OF PATIENTS	PER CENT OF TOTAL GROUPS	NUMBER OF PATIENTS	PER CENT OF TOTAL GROUPS
Gastrointestinal reactions	60	27.0	24	10.8
Cutaneous reactions	15	6.9	2	0.9
Hematopoietic reactions	13	5.9	2	0.9
Electrolyte disturbance	8	3.5	2	0.9
Miscellaneous	1	0.5		
Total	97	43.8	30	13.5

TABLE XI. TOXICITY IN 160 PATIENTS RECEIVING 400 MG. OR LESS PER DAY

TYPE OF REACTION	NUMBER OF PATIENTS	PER CENT OF TOTAL GROUP
Gastrointestinal reactions	32	20.0
Cutaneous reactions	6	3.6
Hematopoietic reactions	3	1.8
Electrolyte disturbance	4	2.4
Miscellaneous reactions	1	0.6
Total	46	28.4

cases including the four in which phenylbutazone was continued.* One patient who discontinued the drug was unable to tolerate the severe symptoms of rheumatoid spondylitis after withdrawal of phenylbutazone and therapy with this drug was again initiated. Serial x-rays showed prompt healing of a duodenal ulcer with antacids and diet management. The patient has continued therapy for 14 months and has remained free of gastrointestinal symptoms.

TABLE XII. PEPTIC ULCER AS A COMPLICATION OF PHENYLBUTAZONE THERAPY

PATIENT	TYPE OF ULCER	PHENYLBUTAZONE DOSAGE (MG. PER DAY)	ULCER NEW OR OLD*	LENGTH OF THERAPY
1	Duodenal	200	New	10 mo.
2	Duodenal	200	New	5 mo.
3	Duodenal	300	Old	2 mo.
4	Gastric	400	Old	1 mo.
5	Duodenal	400	Old	4 mo.
6	Duodenal	400	New	22 mo.
7	Duodenal	400	New	5 mo.
8	Duodenal	400	Old	2 wk.
9	Duodenal	400	Old	1 wk.
10	Duodenal	600-400	New	12 mo.
11	Duodenal	600-400	New	10 mo.
12	Gastric	600-400	New	46 mo.
13	Duodenal	800	Old	3 mo.

*The decision regarding whether the ulcer was "new" or "old" was made after careful clinical questioning by Dr. Fred Kern, Chief of Gastroenterology, University of Colorado School of Medicine. It should be pointed out that conclusive evidence of fresh ulcers by pre- and posttherapy x-rays is not available.

One patient developed a severe gastric hemorrhage and phenylbutazone therapy was stopped. Eight months later the patient died and at autopsy a carcinoma of the stomach was demonstrated.

Cutaneous Reactions.—Fourteen patients in the series developed skin rashes during the period of observation. However, further investigation revealed that in at least 4 cases the rash was not caused by drug therapy. In one case the patient was found to have a contact dermatitis resulting from sensitivity to a detergent used in laundering her garters. In 3 other cases, the rash involved only the wrists and forearms and was probably caused by warm paraffin treatments given in the Department of Physical Medicine.

Of the 10 rashes assumed to be caused by phenylbutazone, 9 were maculopopular and one was petechial. Earlier in the study it was our practice to discontinue the drug in the appearance of any skin lesion. In each of 5 cases so handled, the rash promptly disappeared. In 3 cases, the drug was started again without reappearance of the rash. In 4 cases occurring within the last 2 years, the rash disappeared although the drug was continued.

A more serious type of rash associated with generalized hypersensitivity reaction was not seen in our group of patients. Four deaths have been reported from mucocutaneous reactions occurring during phenylbutazone therapy.[10-13] It

*Since submission of this report for publication, one patient has shown a second episode of gastrointestinal bleeding on phenylbutazone therapy. Gastrointestinal series and gastroscopy revealed a gastric ulcer whereas the previous ulcer had been duodenal.

has been suggested[13] that patients exhibiting skin reactions were likely to develop agranulocytosis later in the course of therapy. This has not been true in the small number of cutaneous reactions encountered in this series.

Hematopoietic Reactions.—Ten deaths have been attributed to blood dyscrasias associated with phenylbutazone therapy, and other nonfatal cases of leukopenia, agranulocytosis, and thrombocytopenia have been described.[13-22] For this reason, careful hematologic observations were made on the patients in this series. No cases of agranulocytosis occurred. Most of the patients who showed any change in the blood picture had a slight depression of the leukocyte count. In 8 patients the count fell below 5,000, the lowest being 2,700, and the drug was temporarily discontinued in all of these patients. In 2 cases, the white count again fell when phenylbutazone was again administered and the drug was therefore permanently discontinued. Mild and transient anemia (3 cases) and thrombocytopenia (2 cases) were occasionally observed. In this series, none of the patients was known to have suffered permanent ill effects from hematopoietic toxicity.

Electrolyte Disturbances.—Edema caused by salt retention has been reported to be a common toxic effect of phenylbutazone therapy.[23] In this series, the patients were screened for evidence of heart disease, and patients with a history of congestive failure were excluded from the study. Many of the patients showed weight gains of from 5 to 10 pounds and in these cases salt was restricted. Eight patients developed edema requiring rigid salt restriction and diuretics. Two of these patients developed moderately severe congestive failure in spite of these measures, and therapy was discontinued.

Miscellaneous Reaction.—One patient was hospitalized during the study because of mental confusion and fatigue. No diagnosis was established and she made a spontaneous recovery. When she again was placed on this drug, these symptoms did not recur.

Deaths.—Five of the patients who have been treated with phenylbutazone have died since coming under observation. Death in one instance was from accidental gunshot wounds and occurred while the patient was being maintained on the drug. The other 4 deaths were caused by carcinoma of the stomach, cirrhosis of the liver, bronchial pneumonia, and coronary occlusion, and in no instance was phenylbutazone toxicity implicated as the cause of death. In the last 4 cases, death occurred at least 6 months after drug therapy was discontinued.

In summary, 97 patients (43.8 per cent) exhibited toxic reactions of some nature while taking phenylbutazone. Of these, 30 patients (13.5 per cent) showed reactions requiring withdrawal of the drug. The total incidence of toxicity was reduced from 43.8 per cent to 28.4 per cent by lowering the drug dosage to 400 mg. of phenylbutazone per day. In no case was it established that phenylbutazone had caused any permanent harm to the patients in this series.

Although all of the patients in the group reported here apparently recovered rapidly from any toxicity produced by phenylbutazone, serious sequelae and death have been reported following the use of this drug. Many of the reported fatal toxic reactions have occurred in patients who received larger doses than now commonly employed, though at least 8 fatal reactions have been reported with

400 mg. per day or less. Little information regarding the over-all frequency of such reactions is available. Mauer[13] has summarized data from 3,934 patients receiving a variety of dosage schedules and found 3 deaths (0.08 per cent) in the total group. The same author reports a total of 24 deaths from the world's literature, 10 which occurred in the United States. If one accepts the reported sales figures of the manufacturers which indicate that 3,000,000 patients have been treated with phenylbutazone[24] in this country, the risk of fatal toxicity does not seem to be prohibitive.

Less serious toxicity has in many cases been controlled by limiting the dosage of the drug to 400 mg. per day and advising the patient to take the drug with meals or with antacids. In spite of such precautions, however, observation of patients undergoing prolonged therapy has revealed a disturbing increase in the incidence of peptic ulcer. Our experience has prompted us to increase the carefulness with which we rule out those patients with a history of gastrointestinal symptoms in selecting subjects for prolonged phenylbutazone therapy. The occurrence of 4 hemorrhages from peptic ulcers emphasizes the need for careful supervision with special attention to symptoms suggestive of ulcer or ulcer complications. All of the patients developing ulcers have responded rapidly to the usual medical therapy; some while continuing to take the drug. No chronic ulcers are known to have been initiated by phenylbutazone therapy.

VOL.
5
1957

SUMMARY

1. The long-term therapeutic value of phenylbutazone (Butazolidin) has been studied in 93 patients with rheumatoid arthritis and objective measurements of therapeutic effectiveness have been made over a shorter period on 20 patients.

2. A method for measuring the degree of joint inflammation has been presented.

3. Of 49 patients treated for periods of 2 to 5 years, 19 (39 per cent) have found this drug to be a satisfactory long-term therapeutic agent in terms of maintaining functional capacity.

4. In a double-blind comparative study, phenylbutazone and cortisone were found to be superior to aspirin in suppression of inflammation and maintenance of functional capacity. Large doses of cortisone were superior to phenylbutazone but the differences were not striking.

5. The natural course of the pathologic process of rheumatoid arthritis as reflected in the joint destruction shown in serial roentgenograms was not arrested by phenylbutazone.

6. The toxic reactions in 222 patients who received phenylbutazone for a variety of rheumatic disorders have been analyzed. In no case was it established that phenylbutazone caused any permanent harm to the patients in this series.

REFERENCES

1. Short, C. L., and Bauer, W.: The Course of Rheumatoid Arthritis in Patients Receiving Simple Medical and Orthopedic Measures, New England J. Med. **238**:142, 1948.
2. Ragan, C.: Rheumatoid Arthritis: The Natural History of the Disease and Its Management, The Musculoskeletal System, New York, 1952, Macmillan Company, p. 206.
3. Duthie, J. J.: The Value of Long-term Conservative Treatment in Rheumatoid Arthritis. Bull. Rheumat. Dis. **4**:54, 1954.

4. Empire Rheumatism Council: Multi-centre Controlled Trial Comparing Cortisone Acetate and Acetyl Salicylic Acid in the Long-term Treatment of Rheumatoid Arthritis, Ann. Rheumat. Dis. **14**:353, 1955.
5. Lansbury, J., and Haut, D. D.: Quantitation of the Manifestations of Rheumatoid Arthritis. IV. Area of Joint Surfaces as an Index to Total Joint Inflammation and Deformity, Am. J. M. Sc. **232**:150, 1956.
6. Beutler, E., and Bergenstal, D. M.: Perforated Duodenal Ulcer With Neutropenia and Death in Patient Receiving Phenylbutazone Therapy, Gastroenterology **25**:72, 1953.
7. McGinley, W. K.: Death Due to Butazolidin, Brit. M. J. **2**:1427, 1952.
8. Benstead, J. G.: Death of Two Patients Treated by Phenylbutazone, Brit. M. J. **1**:711, 1953.
9. Hoffman, Arthur M. (personal communication to E. F. Mauer): The Toxic Effects of Phenylbutzone (Butazolidin), New England J. Med. **253**:404, 1955.
10. Nathan, D. A., Meitus, M. L., Capland, L., and Lev, M.: Death Following Phenylbutazone (Butazolidin) Therapy: Report of a Case, Ann. Int. Med. **39**:1096, 1953.
11. Bluefarb, S. M., and Holt, L.: Erythema Multiforme Bullosum Following Phenylbutazone Therapy, Illinois M. J. **107**:37, 1955.
12. Cone, R. B., Hannigan, C. A., and Tercher, R.: Erythema Multiforme Bullosum Following Phenylbutazone Treatment for Arthritis: Report of a Fatal Case, A.M.A. Arch. Dermat. & Syph. **69**:674, 1954.
13. Mauer, E. F.: The Toxic Effects of Phenylbutazone (Butazolidin) Review of the Literature and Report of the Twenty-third Death Following Its Use, New England J. Med. **253**:404, 1955.
14. Leopold, J. G.: Deaths Due to Butazolidin, Brit. M. J. **2**:1427, 1952.
15. Feldman, L., Cohen, F., and Hirsch, H.: Fatal Thrombocytopenia Purpura Following Phenylbutazone (Butazolidin) Therapy, Illinois M. J. **105**:83, 1954.
16. Procter, J. O., and Evans, F. G.: Toxic Effects of Phenylbutazone, Lancet **1**:1047, 1953.
17. Dilling, N. V.: Fatal Agranulocytosis and Gastric Ulceration Due to Phenylbutazone, Lancet **1**:1230, 1953.
18. Newns, G. R.: Butazolidin, Brit. M. J. **1**:992, 1953.
19. Wood, I. H.: Fatal Case of Agranulocytosis Following Phenylbutazone. Brit. M. J. **1**:802, 1954.
20. Etess, A. D., and Jacobson, A. S.: Fatality Due to Agranulocytosis Following Use of Phenylbutazone (Butazolidin), J.A.M.A. **151**:639, 1953.
21. Steinberg, C. L., Bohrod, M. G., and Roodenburg, A. I.: Agranulocytosis Following Phenylbutazone (Butazolidin) Therapy: Report of a Fatal Case, J.A.M.A. **152**:33, 1953.
22. Rice, H. M.: Death Due to Butazolidin, Lancet. **1**:192, 1953.
23. Kuzell, W. C., Schaffarzick, R. W., Naugler, W. E., Gaudin, G., and Mankle, E. A.: Phenylbutazone: Further Clinical Evaluation, A.M.A. Arch. Int. Med. **92**:646, 1953.
24. 100 Million Patient-Days of Therapy. Editorial Issue, Rheumatology Reviews, The Medical Department, Geigy Pharmaceuticals.

OBSERVATIONS ON NEW SYNTHETIC ANTIRHEUMATIC STEROIDS AND CRITICAL EVALUATION OF PREDNISONE THERAPY IN RHEUMATOID ARTHRITIS

ROGER L. BLACK, M.D., K. LEMONE YIELDING, M.D., AND JOSEPH J. BUNIM, M.D.

BETHESDA, MD.

From the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Md.

(Received for publication Feb. 5, 1957.)

VOL. 5 1957

AS A result of the many adverse side effects that were encountered in the use of the naturally occurring 11, 17-oxygenated steroids, cortisone and hydrocortisone, the need for an antirheumatic agent that would be relatively free of unwanted effects became pressing. Within a short span of 3 years (1954 through 1956) many new 11, 17-oxygenated steroids were synthesized and of these, 5 compounds exhibited biologic activities in adrenalectomized animals that were promising enough to invite careful clinical trial in patients with rheumatoid arthritis. The structural formulas of these 5 steroids are included in Fig. 1 and their biologic activities are listed in Table I.

RELATION OF CHEMICAL STRUCTURE TO BIOLOGIC ACTIVITY OF HYDROCORTISONE ANALOGUES

The side chain and various substituents that a steroid must possess in order to exhibit antirheumatic activity in man have now been defined. It has become evident that the most subtle modifications of the molecular structure of hydrocortisone may result in profound effects on the mineralocorticoid, glucocorticoid, nitrogen antianabolic, and anti-inflammatory activities of the steroid derivatives. As summarized by Fried,[1] the antirheumatic effects of corticosteroid compounds seem to depend upon (1) a 3-keto, 4,5 unsaturated structure in ring A; (2) an oxygen atom at position 11; and (3) a dihydroxyacetone side chain at position 17 (Fig. 1). Modifications of four general types have been made in the molecular structure of hydrocortisone and the specific biologic effects of these changes measured.

1. *The Halogenated Derivatives.*—The halogenation of cortisone or hydrocortisone produced a family of interesting compounds. When the heavier halogens, iodine and bromine, were substituted at the 9-alpha position of cortisone acetate, the glucocorticoid activity was reduced to one-tenth and one-third, respectively, that of the parent steroid. When, however, the lighter halogens, chlorine and fluorine, were substituted, a derivative was produced which was 4 and 11 times, respectively, more potent than the halogen-free steroid.[2]

2. *Dehydrogenation of Carbons in the Steroid Nucleus.*—As mentioned, the 4, 5 unsaturated bond in the hydrocortisone molecule is a prerequisite for anti-inflammatory activity, but introduction of a double bond between carbons 6 and 7 results in a loss of this effect.[1] Yet the introduction of such a bond between carbons 1 and 2 (prednisone and prednisolone) produces a fourfold increase in the antirheumatic potency of the analogue without increasing the mineralocorticoid effect. This configuration also imparts to the compound enhanced glycogen deposition potency that produces little change in the effect on nitrogen metabolism as compared to the parent compound.

TABLE I. RELATIVE POTENCIES OF SYNTHETIC 11, 17-OXYGENATED STEROIDS

	IN ADRENALECTOMIZED RAT			IN MAN		
	SODIUM RETENTION*	GLYCOGEN DEPOSITION†	ANTI-INFLAMMATORY EFFECT‡	SODIUM RETENTION	ANTI-RHEUMATIC EFFECT	ADRENAL SUPPRESSION§[10] DOSE IN MG.
9α-Fluorohydrocortisone	5 x DOCA (22)	13 x F (22)	7 x F (23)	50 x F (6)	10 x F (7)	2.5
Prednisone and Prednisolone	Almost none (22)	3 x F (22)	3 x F (23)	Less than F (12)	3-4 x F (12)	30
Δ^{1},9α-Fluorohydrocortisone	5 x DOCA (22)	50 x F (22)	14 x F (23)	50 x F (6)	15 x F (8)	1.5
Triamcinolone	No sodium retention properties (5)	15-36 x F (5)	—	None observed (11)	4 x F (11)	—

F=hydrocortisone; DOCA=desoxycorticosterone acetate.

*Measured as urinary sodium output in fifth postoperative day of adrenalectomized 140 to 150 Gm. male Sprague-Dawley rats, during 4-hour period following administration of test steroid after 5 ml. oral dose of 0.9 per cent sodium chloride solution.

†Measured as glycogen deposited in livers of adrenalectomized 140 to 160 Gm. male Sprague-Dawley rats 5 days after operation and 7 hours after appropriate dose of steroid.

‡Measured as weight of dried granulation tissue that developed in 7 days about 2 subcutaneously implanted cotton pellets during steroid administration in adrenalectomized rats.

§Milligrams of steroid required to completely suppress hydrocortisone levels in plasma, 8 to 10 hours after the single oral dose given at midnight.

3. *Methyl Derivatives.*—The addition of a methyl group to carbon 2 produces important changes in the biologic activity of the steroid. Liddle, Richard, and Tomkins[3] described interesting structure-function relationships of a group of "2-methyl" compounds. This chemical modification results in an enhancement of the mineralocorticoid effects of steroids having an 11-beta hydroxy group (hydrocortisone and 9-alpha fluorohydrocortisone) yet imparts a diminished mineralocorticoid effect to the 11-ketosteroids (cortisone). No significant change in effect on nitrogen metabolism results from the addition of the methyl substituent. Addition of a methyl group to carbon 6, however, results in an increased anti-inflammatory effect but no increase in sodium retention.[4]

4. *Changes in Hydroxyl Groups.*—The loss of the hydroxyl group at position 17-alpha results in a decrease of glucocorticoid effect by a factor of 2 and a

twofold increase of sodium-retaining properties. In contrast, loss of this group at carbon 21 causes a seven-fold loss of glucocorticoid activity and a decrease of sodium effect by a factor of 15.[1] It has been demonstrated recently that when an hydroxyl substituent is added to carbon 16 of delta-1, 9-alpha fluorohydrocortisone, the marked sodium-retaining and potassium-losing effects of the parent compound are overcome but the anti-inflammatory property is partially retained.[5]

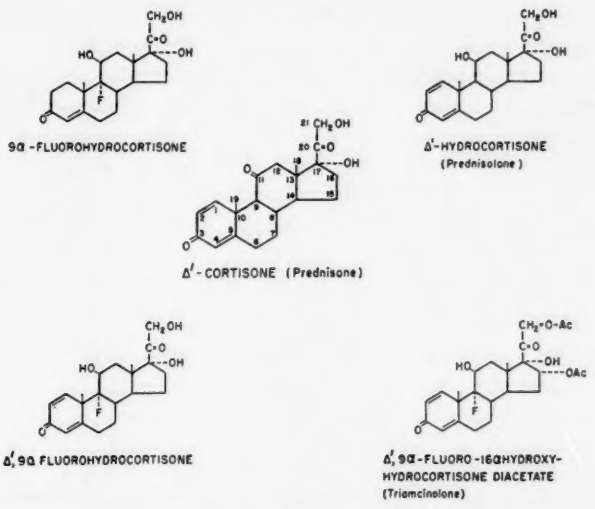

Fig. 1—Synthetic steroids with potent antirheumatic properties.

EFFECTS OF SPECIFIC SYNTHETIC STEROIDS

9-alpha Fluorohydrocortisone.—In 1954, Fried and Sabo synthesized a fluorinated hydrocortisone which proved to have an enhanced glycogen depositing effect in the adrenalectomized rat that was 13 times that of hydrocortisone. The effect in man on producing true glycosuria was enhanced 20 times that of hydrocortisone and on sodium retention was 50 times that of the parent steroid.[6]

Boland and Headley[7] reported results of clinical trials on 9-alpha fluorohydrocortisone in 13 patients with rheumatoid arthritis. These investigators found effective suppression of disease with 4 to 8 mg. daily and noted that this steroid, on a weight basis, was about 10 times more effective than hydrocortisone as an antirheumatic agent. The appearance of edema in 12 of the 13 patients and an increase in blood pressure of 6 caused discontinuation of the drug. This potent and troublesome side effect of sodium retention has discouraged further clinical trials on rheumatoid patients.

This steroid is an unusually potent agent for suppression of pituitary corticotropin secretion. Only 1 to 2 mg. administered in single dose or in divided dosage over a 24-hour period maximally depresses plasma hydrocortisone levels.

Delta-1, 9-alpha Fluorohydrocortisone.—The combination of dehydrogenation of carbons 1 and 2 (as in prednisone) and the introduction of a fluorine atom at carbon 9 (as in 9-alpha fluorohydrocortisone) resulted in a new compound,

VOL.
5
1957

delta-1, 9-alpha fluorohydrocortisone. Sodium retention in man, following administration of this steroid, is about 50 times that of hydrocortisone or the same as 9-alpha fluorohydrocortisone.[6] Although clinical trials in patients with rheumatoid arthritis revealed an antirheumatic effect 15 times that of hydrocortisone, the drug was found to cause severe sodium retention and potassium loss. Black and associates[8] reported experience with this drug in 10 rheumatoid patients and one normal control subject. Doses from 2 to 6 mg. per day were required to suppress signs and symptoms of arthritis. Villa and co-workers[9] administered daily doses of 4 to 10 mg. to 3 rheumatoid arthritis patients and attained beneficial responses but again with severe sodium retention and potassium loss. Each group of investigators reported development of abnormal glucose tolerance in one patient following administration of this steroid. Because of the potent effects on sodium and potassium metabolism, it appears doubtful that this drug will be useful in the management of rheumatic diseases. However, doses as low as 1.5 mg.[10] have been effective in suppressing pituitary corticotropin secretion and hence hydrocortisone synthesis. This is reflected in the reduction of plasma hydrocortisone to levels that cannot be measured. For this reason, this steroid has proved to be a useful agent in several research problems.

Triamcinolone (Delta-1, 9-alpha Fluoro, 16-alpha Hydroxy Hydrocortisone Diacetate).—A further alteration in the steroid structure was accomplished by the addition of an hydroxyl group at the 16 carbon position and by acetylation of this compound in 16 and 21 positions, resulting in the formation of delta-1, 9-alpha fluoro, 16-alpha hydroxy hydrocortisone diacetate (or triamcinolone).[5] This modification of the steroid structure resulted in overcoming the sodium-retaining effect of the 9-alpha fluorine atom. Subjects receiving this steroid did not retain sodium or lose potassium excessively. Balance studies reported by Hellman and co-workers[11] showed actual sodium loss when given to patients in doses of 12 mg. daily. The antirheumatic potency was similar to prednisone or 4 times that of hydrocortisone (per weight of compound employed). This has been consistent with our experience in patients with rheumatoid arthritis.

The side effects have been few and minor in the too brief period of clinical trials with this drug. In general, patients have tended to lose rather than gain weight and there has been noted less epigastric pain. Profuse sweating accompanied by waves of warmth has been a prominent complaint among postmenopausal women. Purpuric cutaneous manifestations have been noted in one of our patients who experienced the same phenomenon when taking prednisone.

As yet, experience with this compound has been much too limited to make any definite statements concerning frequency or severity of side effects as compared to prednisone.

CLINICAL EXPERIENCE WITH PREDNISONE THERAPY IN RHEUMATOID ARTHRITIS

Of the synthetic steroids tested to date, prednisone and prednisolone have had by far the widest use. In the two years since these compounds were introduced (November, 1954), several hundred scientific papers reporting results of laboratory and clinical studies have appeared.

Pattern of Favorable Response.—The principal advantage of these steroids is that in therapeutic doses they do not cause sodium retention or significant potassium loss in the vast majority of cases. Their antirheumatic potency is 3 to 4 times that of cortisone or hydrocortisone (per weight of compound employed). Patients with rheumatoid arthritis who have stopped responding to prolonged administration of the parent steroid again exhibit marked improvement when prednisone is given. The pattern of response is similar to that of cortisone. Subjective and objective improvement of the arthritis is accompanied by reduction in the erythrocyte sedimentation rate (ESR), disappearance of C-reactive protein, eosinopenia, increase in serum albumin and decrease in serum globulin, increase in hematocrit and hemoglobin concentration, striking reduction in the inflammatory reaction of affected synovial lining, and suppression of anterior pituitary secretion of corticotropin with fall in plasma hydrocortisone concentration and urinary excretion of corticoids and 17-keto steroids.[14] Although the initial improvement which follows institution of prednisone diminishes somewhat as administration is prolonged, the impressive gains made in increased functional capacity are sustained (Table II).

VOL.
5
957

TABLE II. IMPROVEMENT IN FUNCTIONAL CAPACITY OF TEN PREDNISONE-TREATED PATIENTS WITH RHEUMATOID ARTHRITIS OBSERVED FOR 17 TO 27 MONTHS

BEFORE TREATMENT*		AFTER 17-27 MONTHS OF THERAPY			
CLASS	NUMBER OF PATIENTS	CLASSES			
		I	II	III	IV
I. Complete functional capacity	0	—	—	—	—
II. Capacity adequate, but with discomfort	2	2	—	—	—
III. Can perform few or no normal activities	6	4	2	—	—
IV. Incapacitated. Wheel chair or bedridden	2	—	1	1	—

*Before prednisone was begun, 4 patients had been receiving hydrocortisone, 3 cortisone, and 3 only aspirin.

Limitations and Hazards.—The limitations of prednisone therapy are those shared by other suppressive antirheumatic agents such as salicylates, gold, phenylbutazone, cortisone, hydrocortisone, and corticotropin. When the drug is discontinued, the arthritis flares unless the disease is in remission. The natural course of the disease is not fundamentally altered. Destruction of cartilage and bone may advance even though the clinical signs and symptoms of arthritis recede and the ESR remains lowered or normal.

The first report on the results obtained with prednisone therapy in rheumatoid arthritis included the reservation "that serious side-effects, not apparent when a small group of patients is first studied, may yet emerge as experience with a new therapeutic agent increases."[12] Unfortunately, this reservation has proved to be amply justified. Major adverse reactions were reported 6 months after the first paper appeared.[13] At the end of a 2-year observation of a group of

39 patients with rheumatoid arthritis the increasing incidence of serious side effects (Tables III to VII) continues to demand extreme caution and arouse serious concern. In contemplating institution of prolonged therapy in rheumatoid arthritis, or in any other disease, it is imperative that the physician carefully estimate the risks involved. The beneficial results that one has reason to expect from steroid therapy and the hazard of withholding treatment should clearly outweigh the risk of serious adverse effects. When decision is made to embark on steroid therapy, the overriding importance of dosage should receive principal consideration. It has become a truism in steroid therapy that as the dosage increases, the hazard is enhanced.

Adverse Effects.—This report includes two groups of patients; those who were continually and closely followed by us for a period of two years (15 patients), and those who were observed in the Clinical Center for a period of several weeks to months, then discharged to the care of the referring physician and not followed by us (24 patients). The adverse effects observed in the first group are listed in Table III. Data in the remaining tables are based on the combined groups which total 39 patients. Of these 39 patients, 3 were below the age of 30, 6 were in the fourth decade of life, 10 in the fifth decade, 11 in the sixth, and 9 in the seventh. The duration of rheumatoid arthritis was less than one year in 2 patients, between 1 and 4 years in 8 patients, between 5 and 9 years in 14 patients, between 10 and 19 years in 12 patients, and 20 years or longer in 3 patients. Twenty-five patients were women.

TABLE III. UNDESIRABLE SIDE EFFECTS IN 15 PREDNISONE-TREATED PATIENTS WITH RHEUMATOID ARTHRITIS OBSERVED FOR TWO YEARS

SIDE EFFECTS	NUMBER OF PATIENTS
Facial rounding	14
Hirsutism	10
Cutaneous purpura or ecchymosis	10
Epigastric pain	9
Insomnia and restlessness	9
Increased sweating	7
Fractures (See Table V)	5
Peptic ulcer (see Table VI.)	4
Mental changes	4
Decreased glucose tolerance	3
Weakness and fatigue	3
Acneform eruption	2

Several patients in this group experienced multiple undesirable side effects.

In the group of 15 patients, hirsutism was troublesome in 10 patients, especially in women. Purpura and ecchymosis were noted in 10 patients. This sign occurred usually after several months of therapy. The patients' main complaint was cosmetic, for none of these patients exhibited evidence of blood loss. Bleeding time, coagulation time, and platelet counts were normal in all 7 patients with purpura in whom these determinations were made. Prothrombin time values and ascorbic acid concentration in the blood were also normal. Increased capillary fragility was demonstrated by a positive Rumpel-Leede phenomenon in 6 of 7 patients.

Epigastric pain, insomnia, and restlessness were disturbing to some patients. Increased sweating was noted by 7 patients and was usually accompanied by flushing of the skin occurring 4 to 10 times daily. Most women experiencing this reaction were at or past the menopause; one patient, however, was menstruating regularly.

A decrease in glucose tolerance was demonstrated in 3 of 9 patients in whom determinations were made before and after prednisone administration. In addition to these, two patients, abnormal before treatment, continued to show defective tolerance. None of the patients in this group demonstrated fasting hyperglycemia or glucosuria. Three other patients, in whom pretreatment glucose tolerance tests were not performed, showed abnormal glucose tolerance on prolonged prednisone therapy.

Other minor side effects included weakness and fatigue in 3 patients and acneform eruptions in 2.

Fractures.—Pathologic fractures have occurred in 21 per cent of the combined group (Tables IV and V). Six of the 8 patients who sustained fractures were older than 50 years. It is noteworthy that the disease in all cases was of many years' duration. Seven of the 8 patients had rheumatoid arthritis for 10 years or longer. The dosage of prednisone at the time of the fracture varied between 15 and 30 mg. Vertebral, rib, pelvic, and femoral fractures occurred. It is also noteworthy that all but one of the patients who developed fractures were women. This compares with the experience of Bunim, Ziff, and McEwen[14] who followed 59 patients (32 women and 27 men) on long-term cortisone therapy and noted the incidence of 4 fractures—all in female patients. Howell and Ragan[15] reported 6 vertebral compression fractures in 68 rheumatoid arthritis patients receiving prolonged cortisone therapy. All but one of these occurred in women of menopausal or postmenopausal age.

TABLE IV. SERIOUS SIDE EFFECTS AND COMPLICATIONS IN 39 PREDNISONE-TREATED PATIENTS WITH RHEUMATOID ARTHRITIS OBSERVED FOR VARYING PERIODS UP TO TWO YEARS

SIDE EFFECTS		NUMBER	PER CENT
Fractures (see Table V)		8	21
Mental changes		6	16
Psychosis	2		
Transitory depression	4		
Peptic ulcer (see Table VI)		6	16
Polyarteritis nodosa		4	10
Overwhelming intercurrent infection		1	3

Several patients in this group experienced more than one of the serious side effects listed.

Comment.—What factors may have contributed to this high incidence of fractures? Prednisone therapy may be associated with a higher fracture rate than cortisone or hydrocortisone. The long duration of disease and the antecedent, long-term administration of another steroid may have predisposed or "prepared" the skeleton for this complication. The dosage may have been too high.

Six of the 8 patients listed in Table V had received cortisone or hydrocortisone prior to prednisone, 2 for longer than 4 years. Although prolonged steroid

administration may have produced considerable osteoporosis, the fact remains that only one of these 6 patients had experienced a fracture while taking the parent steroids. In light of our present knowledge, administration of prednisone in greater dosage than 15 mg. daily exceeds the limits of prudence and reasonable safety. In certain circumstances, however, the physician may not be free to determine dosage. For example, a switch to prednisone may be contemplated in a patient who had received cortisone for one or more years. Reduction of prednisone dosage to less than one-fourth the former cortisone dosage might produce difficulties that the patient could not tolerate. Nevertheless, this should not deter the physician from the ultimate goal of limiting prednisone dosage to relatively safe levels.

TABLE V. FRACTURES OCCURRING IN A GROUP OF 39 PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH PREDNISONE

PATIENT	AGE AND SEX	DURATION OF ARTHRITIS (YR.)	DURATION OF OTHER STEROID THERAPY PRIOR TO PREDNISONE	FRACTURE ON PREVIOUS STEROID THERAPY	DAILY DOSE OF PREDNISONE AT TIME FRACTURE OCCURRED (MG.)	DURATION OF PREDNISONE THERAPY AT TIME FRACTURE OCCURRED (MO.)	SITE OF FRACTURE
G. A.	67 F.	10	2 mo.	None*	15	5	Dorsal vertebrae V and VIII
Z. W.	57 F.	11	11 mo.	None	20	4	Dorsal vertebra VIII
O. B.	58 F.	10	None	None	15	9	Dorsal vertebra VII; pubis
						12	Femur
A. D.	42 F.	15	50 mo.	Dorsal vertebrae VIII and several ribs	30	7	Dorsal vertebra V and several ribs
E. F.	26 F.	10	52 mo.	None	20	9	Pubis and ischium
D. R.	67 M.	5	9 mo.	None	15	14	Lumbar vertebra I
E. Z.	67 F.	14	None	None	25	14	Dorsal vertebrae V and VIII
T. K.	54 F.	17	2 yr.	None	20	15	Dorsal vertebra XI; Lumbar I, III, IV, and V

*Sustained fracture of lumbar vertebra I before receiving any steroids.

The mechanism for osteoporosis associated with steroid administration is not completely understood. The best explanation thus far advanced is Albright's concept that osteoporosis is a disease of protein matrix of bone and not of bone itself. The adrenal oxysteroids, which are antianabolic, interfere with matrix formation while bone resorption proceeds at normal rate. The effectiveness of estrogen and androgen therapy in protecting the skeleton during steroid therapy

has not been conclusively demonstrated. The role of dietary calcium in the pathogenesis and correction of osteoporosis needs to be re-evaluated.

Mental Changes.—Mental changes occurred in 6 of 39 patients receiving prednisone. In only two patients, however, did a frank psychosis develop, which persisted and required institutional care. In the other 4 patients, contact with reality remained, although severe instability, unreasonable behavior, and unusual activity were prominent. These 4 patients improved upon continued (but usually decreased) steroid dosage.

Quarton and co-workers[16] have carefully reviewed the question of steroid-induced mental disturbances and stated that a satisfactory explanation for these disturbances is not yet available.

Psychoses during steroid therapy have been reported in from 0 to 10 per cent of cases[15] and average about 5 per cent.[17] In mild cases of mental aberration, steroid therapy can often be safely continued at slightly lower maintenance levels, but occasionally a severe psychotic depression will necessitate discontinuing steroid medication.

VOL.
5
1957

Peptic Ulcers.—Sixteen per cent of our patients developed peptic ulcers during prednisone therapy (Table VI). One of the 6 patients had an ulcer previously that healed on medical treatment. In one patient the ulcer was symptomless and was detected by routine radiographic examination of the duodenum. The dosage of 30 mg. daily in 3 patients requires special comment. Two of these patients were among the first 7 to be treated with prednisone and the level of safe dosage had not yet been determined. The ulcers developed during the third and fourth week of therapy. A third patient was discharged from the hospital taking 15 mg. daily and was instructed not to exceed this dose. Because of past history of ulcer, prophylactic ulcer regimen was implemented. While at home, the patient took by error 30 mg. daily and after several weeks was readmitted bleeding briskly.

Three of the 6 patients who developed peptic ulcers recovered even though prednisone was continued; the doses were lowered and antiulcer regimens were prescribed. Two patients died of hemorrhage; one with and the other without the benefit of gastrectomy; both patients had been receiving antiulcer treatment. Their cases are reported in detail in another section of this paper.

The important relationship between size of steroid dosage and incidence of peptic ulcer in patients with rheumatoid arthritis is evident from results observed by Kern, Clark, and Lukens.[18] Three of 14 (21 per cent) prednisone-treated patients developed peptic ulcers when the daily dose was 20 mg. or greater, whereas none of 54 patients developed ulcers when the daily dose was limited to 15 mg. or less.

Is the incidence of peptic ulcer higher in patients treated with prednisone than cortisone? Data available at present are not adequate to permit valid statistical analysis. Boland observed that when therapy in 109 patients with rheumatoid arthritis was switched from hydrocortisone to prednisone the incidence of gastric complaints simulating those that accompany peptic ulcer increased sixfold, from 5.5 to 31 per cent.[19] In contrast, Howell and Ragan[15] reported that the incidence of peptic ulcers in 68 patients treated with cortisone and observed for 4 years was 26 per cent.

TABLE VI. PEPTIC ULCERS OCCURRING IN A GROUP OF 39 PREDNISONE-TREATED PATIENTS WITH RHEUMATOID ARTHRITIS

PATIENT	AGE AND SEX	SITE	HISTORY OF PRECEDING ULCER	DAILY DOSE AT TIME ULCER DETECTED (MG.)	DURATION OF TREATMENT AT TIME ULCER DETECTED (WK.)	DIGESTIVE SYMPTOMS	OUTCOME
A. B.	32 F.	Duodenal	No	30	3	Epigastric pain	Improved, steroid discontinued
F. J.	16 M.	Duodenal	No	30	4	None	Improved, steroid continued at reduced dosage. Antiulcer regimen followed
E. Z.	67 F.	Duodenal	No	25	10	Epigastric pain	Improved, steroid continued at reduced dosage. Antiulcer regimen followed
Mc. R.	67 M.	Duodenal	Yes	30*	12	Epigastric pain	Died, massive hemorrhage (Gastrectomy not done)
A. D.	42 F.	Duodenal	No	20	40	Epigastric pain	Improved, steroid continued at reduced dosage. Antiulcer regimen followed
T. K.	54 F.	Gastric	No	20	100	Epigastric distress and nausea	Massive hemorrhage. Gastrectomy done, died one hour postoperatively

*This dosage was taken by the patient in error while he was followed in the outpatient clinic. He was instructed to take 15 mg. daily.

Massive hemorrhage from peptic ulcer or a perforated ulcer may lead to sudden death. The most effective measure for reducing the incidence of ulcers is to reduce the daily dose of prednisone to 15 mg. or less. Patients receiving 15 mg. or more daily should be urged to accept a full ulcer regimen consisting of bland diet, frequent feedings, antiacid and anticholinergic drugs. Patients who complain of epigastric pain should be examined radiographically for peptic ulcer. In addition, the stool should be tested for occult blood and the hematocrit measured frequently. If an ulcer is detected, and gastrointestinal bleeding continues despite antiulcer therapy, prednisone dosage should be further reduced or completely discontinued. If massive hemorrhage should occur, the patient should be prepared for surgery by adequate transfusions, hydrocortisone intravenously (50 to 100 mg.) if immediate surgery is contemplated, and, in addition, cortisone acetate intramuscularly (50 mg. every 8 hours) beginning before surgery and continuing for several days postoperatively. Prednisone alone may not afford adequate protection against postoperative adrenal cortical failure. A history of previous peptic ulcer is a relative though not absolute contraindication to steroid therapy.

VOL.
5
1957

Polyarteritis Nodosa.—During the past 18 months we have observed the occurrence of polyarteritis nodosa in 4 of 39 patients with rheumatoid arthritis treated with prednisone. In two instances the diagnosis was established by biopsy and in two by necropsy studies. In 3 cases the vasculitis may have developed while the dosage was being tapered; in the fourth, the dose had been maintained at a constant level.

Three of the 4 patients died. In one, death was directly related to the vascular lesions; the patient died of hemorrhage from an aneurysm of an inflamed intrahepatic artery. In a second patient death followed massive hemorrhage from duodenal ulcer and at necropsy disseminated arteritis was discovered. The final illnesses in a third were carcinoma of the breast and congestive heart failure. Necropsy studies revealed rheumatoid heart disease with coronary arteritis, mitral and tricuspid valvulitis, and interstitial myocarditis. The coronary vessels were not severely damaged nor occluded. There were no stigmata of rheumatic heart disease. The fourth patient is still receiving prednisone (15 mg. daily) and is in good functional state (Class II) at present, 12 months after a lesion indistinguishable from polyarteritis nodosa was found in biopsy of the gastrocnemius muscle.

The occurrence of polyarteritis nodosa in rheumatoid arthritis treated and untreated with adrenal steroids, the sites at which these vascular lesions are found, the histologic relationship of rheumatoid arteritis to polyarteritis nodosa, the pathologic significance of polyarteritis nodosa in rheumatoid arthritis, and the role of steroid therapy in the pathogenesis of necrotizing angiitis in rheumatoid arthritis are discussed in the paper on "Vascular Lesions in Rheumatoid Arthritis" which is published elsewhere in this symposium.[20]

How to treat a patient with rheumatoid arthritis who has developed polyarteritis nodosa during steroid administration presents a therapeutic challenge. It seems reasonable to attempt to withdraw steroids very gradually, reducing the dose in decrements of 1 mg. every 7 to 10 days and substituting other suppressive

TABLE VII. ANALYSIS OF 6 DEATHS AMONG 39 PATIENTS WITH RHEUMATOID ARTHRITIS TREATED WITH PREDNISONE

PATIENT	AGE AND SEX	DURATION OF DISEASE	STAGE OF ARTHRITIS	DURATION OF OTHER STEROID THERAPY PRIOR TO PREDNISONE	DURATION OF PREDNISONE THERAPY (MO.)	DAILY MAINTENANCE DOSE (MG.)	INTERVAL FROM STOPPING PREDNISONE TO DEATH	MAJOR ADVERSE EFFECTS OR COMPLICATIONS OF PREDNISONE THERAPY	TERMINAL DISEASE CONTRIBUTING TO DEATH	COMMENTS
J. M.	64 M.	30 yr.	Far advanced (Stage IV)	6 mo.	12	30	None	Polyarteritis nodosa*	Duodenal ulcer with massive hemorrhage	Patient had been receiving prophylactic antiulcer regimen; by error had been taking twice the recommended dose
T. K.	54 F.	17 yr.	Advanced (Stage III)	2 yr.	15	20	None	Fracture of 5 vertebrae (see Table V)	Two gastric ulcers with massive hemorrhage	X-ray of stomach and duodenum was negative few weeks prior to hemorrhage
G. B.	43 F.	10 yr.	Advanced (Stage III)	11 mo.	18	17.5	None	Hypertension; polyarteritis nodosa	Abdominal hemorrhage from ruptured hematoma of liver resulting from vascular necrosis	On cortisone developed hypertension, glycosuria and psychosis; latter two did not recur on prednisone
D. W.	55 F.	16 yr.	Advanced (Stage III)	2 mo.	11	17.5	None	None	Pneumonia and meningitis	Admitted two days before death; failed to respond to antibiotics
J. S.	71 M.	6 mo.	Advanced (Stage III)	None	6	25	6 wk.	Hyperglycemia; mental changes	Old and recent cerebral infarctions	Death most likely unrelated to prednisone
M. H.	65 F.	7 yr.	Far advanced (Stage IV)	6 wk.	18	15 to 30	None	None	Carcinoma breast; congestive heart failure	Death most likely unrelated to prednisone

*It is recognized that polyarteritis nodosa may be related to rheumatoid arthritis and not necessarily due to steroid administration.

VOL. 5 1957

agents concomitantly. In most cases, however, it will be found difficult or impossible to withdraw steroids completely and the patient will have to be maintained at the lowest tolerable dose. Repeated attempts to discontinue steroids should be made periodically.

Deaths During Prednisone Administration.—Six of 39 patients died during the past year (1956). Of these 6 patients, 2 (D. W. and J. S.) had been discharged from the Clinical Center and returned to the referring physician for continued care. In one case (T. K.) prednisone therapy had been initiated by the referring physician 15 months before admission. The clinical data are recorded in Table VII and a summary of each case is given below. The ages of these patients ranged from 43 to 71 years of age. The arthritis was of long duration in all but one case. Duration of prednisone therapy was from 6 to 18 months. The daily dose varied from 15 to 30 mg. Five patients had received cortisone or hydrocortisone before prednisone for periods of 6 weeks to 2 years. In 2 cases (J. S. and M. H.) death most likely was not related to prednisone administration.

VOL.
5
957

By the end of 1953, after cortisone, hydrocortisone, and corticotropin had been used in rheumatoid arthritis for 5 years, Hench and Ward[21] could find references to 32 rheumatoid patients who died from various causes during or sometime after end of hormonal therapy. These workers were of the opinion that of the 32 deaths, 9 were definitely or probably related to treatment and the relationship of the remainder "was either possible but doubtful, entirely coincidental, or not clear."

In a series of 64 patients with rheumatoid arthritis treated with cortisone and observed for 4 years, Bunim and associates[14] reported 5 deaths; 3 were not related, one was possibly and another probably related to cortisone administration. The last-mentioned patient died of an overwhelming intercurrent infection as did one patient in the present series (D. W.)

Howell and Ragan[15] reported 11 deaths in a group of 68 rheumatoid patients treated with cortisone, corticotropin, or hydrocortisone during a period of 6 months to 5½ years. Of these 11 deaths, the major contributing factors were bleeding or perforating peptic ulcers in 3 cases, malignant rheumatoid arthritis in 2, and intercurrent infection (pneumonitis and acute bacterial endocarditis) in 2 cases. Of the 6 deaths in the present report (Table VII) 2 resulted from bleeding peptic ulcers, one from necrotizing vasculitis (polyarteritis nodosa), and one from intercurrent infection (pneumonia and meningitis).

The clinical summary and necropsy findings in each of the six cases follow.

CASE 1.—J. M., a 64-year-old white man, was admitted to the Clinical Center Nov. 28, 1955, incapacitated with rheumatoid arthritis, of 30 years' duration, involving many joints. His weight had fallen by 50 pounds. There was a history of acute coronary occlusion 3 years previously followed in 6 months by duodenal ulcer that healed with medical treatment. The arthritis failed to respond to aspirin and cortisone. For 6 months before admission the patient received prednisone (daily doses varied from 5 to 30 mg.) without decided relief. Examination revealed advanced, destructive, deforming, active, peripheral rheumatoid arthritis, subcutaneous nodules, enlarged lymph nodes in axilla and groin, enlarged heart with a soft apical systolic murmur, a slightly enlarged liver, and hypertension. Electrocardiogram showed changes consistent with old myocardial infarct. Laboratory results included an elevated ESR, a markedly elevated sheep cell agglutination titer (1:8,192), and a negative L.E. Cell test.

Prednisolone therapy was started on Dec. 25, 1955, in daily doses of 30 mg. and gradually tapered in 2 weeks to 20 mg. During the sixth week of therapy the patient complained of epigastric pain. Roentgenographic studies revealed an esophageal hiatus hernia but no evidence of gastric or duodenal ulcer. The daily dose of prednisolone was lowered to 15 mg. and an antiulcer regimen was instituted consisting of frequent feedings of a bland diet, propantheline (pro-Banthine), and aluminum hydroxide gel. The patient was discharged improved on this therapeutic program on May 4, 1956.

On June 30, 1956, he complained of marked weakness, epigastric pain and melena. It was discovered that since discharge the patient had been taking, in error, 30 instead of 15 mg. daily. He was readmitted and given several transfusions immediately. Roentgenograms of stomach and duodenum were interpreted as showing no ulcer; the esophageal hiatus hernia previously reported was again noted. The patient's general condition was too precarious to permit surgery. With medical treatment his condition improved markedly. In view of the favorable course it was decided to delay operation in order to better prepare the patient for surgery. On July 6, he suddenly lapsed into shock and died in a few minutes.

Necropsy was done by Dr. Leon Sokoloff. The principal findings consisted of chronic duodenal ulcer with massive gastrointestinal hemorrhage; recent arteritis in hypothalamus, pancreas, right adrenal gland, spermatic cord, seminal vesicle, sciatic nerve, and right sternoclavicular joint; generalized, severe atherosclerosis, and a fibrous scar in the myocardium.

VOL 5 195

Comment: It seems likely that the duodenal ulcer was activated by prednisone. Unfortunately, the patient took twice the prescribed dose of steroid, by error, for 8 weeks. The roentgenograms taken soon after readmission may have failed to reveal the ulcer because a blood clot filled the crater. It was reasoned that bleeding originated from the site of the esophageal herniation and the surgery required to correct this lesion would be relatively formidable. At necropsy no ulcer was found in the esophagus. Had the roentgenograms indicated a duodenal ulcer, surgery would have been attempted when the patient had rallied from the first hemorrhage. The disseminated arteritis was not suspected during life since there were no clinical signs of such a lesion.

CASE 2.—T. K., a 54-year-old white woman, was admitted to the Clinical Center on May 3, 1956, with chronic, progressive, peripheral rheumatoid arthritis of 17 years' duration. During this long course of illness, salicylates, gold compounds, and phenylbutazone had been administered for varying intervals with moderate improvement. Corticotropin and cortisone had been given but were discontinued because edema developed. In March, 1955, 15 months before admission, the patient's physician had started prednisone therapy and varied the dose from 40 to 20 mg. daily. Fracture of 5 vertebral bodies had occurred shortly before the patient was referred to the Clinical Center. She was admitted for study of the effects of administration of androgens, estrogens, and a diet of high calcium content. On repeated questioning she denied epigastric pain. X-ray of the stomach and duodenum was normal in February, 1956.

Examination on admission revealed widespread peripheral rheumatoid arthritis, purpuric spots on the hands and forearms, kyphosis with prominent lower dorsal angulation, and edema of the feet and legs. The ESR was 15 mm. per minute (Westergren), sheep cell agglutination test was positive, and L.E. cell test was negative. Roentgenograms of the spine showed collapse of the eleventh dorsal vertebra, and first, third, fourth, and fifth lumbar vertebrae. Roentgenograms of the peripheral joints showed destruction of articular cartilage and bone, and ankylosis of several joints.

When an attempt was made to discontinue prednisone the patient developed life-threatening withdrawal symptoms. Prednisone was resumed after a lapse of 24 days and the patient promptly improved. The daily dose was reduced to 15 mg. in August, 1956, but because of unsatisfactory results it was restored to 20 mg. by October, 1956. At this time the patient began to complain of postprandial nausea and an antiulcer regimen was prescribed. This consisted of methantheline (Banthine) and frequent feedings of bland diet. The digestive symptoms were not relieved.

Roentgenogram on December 17 revealed hiatus esophageal hernia but no definite ulcer of the stomach or duodenum. Prednisone was continued in dosage of 20 mg. daily. On December 18, methantheline was discontinued because patient complained of dryness of mouth and difficulty in swallowing. Aluminum hydroxide and milk of magnesia were given every two hours. On December 31, the patient vomited approximately one pint of blood. The blood loss continued for the next 30 hours. Fourteen pints of whole blood were transfused within 36 hours and the patient was prepared for operation by administration of a total of 175 mg. of hydrocortisone intravenously and 50 mg. of cortisone acetate intramuscularly. A gastrectomy was done 36 hours after onset of hematemesis. At operation two bleeding gastric ulcers were found; one in the prepyloric region and one on the lesser curvature. During surgery the patient's general condition improved strikingly. The blood pressure and pulse rate became normal. She was observed in the recovery room for one hour and her condition was good. Immediately after she was returned to her room she suddenly died.

Necropsy was done by Dr. Frederick H. Fox. No evidence of postoperative gastrointestinal bleeding was found. Gross examination failed to reveal the cause of death. Microscopic sections were not yet available at the time this report was written.

OL.
5
957

Comment: The gastric ulcers and the fractured vertebrae were most likely related to prolonged prednisone administration. When the patient was admitted to the Clinical Center, attempts to discontinue the steroid or even to reduce the daily dose to 15 mg. were abandoned because the patient could not tolerate the effects. The cause of death is unknown. Adrenocortical failure does not seem likely since the patient had received large amounts of hydrocortisone and cortisone parenterally. The suddenness of death suggests cardiac arrhythmia.

CASE 3.—G. B., a 43-year-old Negro woman, was admitted to the Clinical Center on Dec. 9, 1954, with advanced rheumatoid arthritis of 10 years' duration. A few months after onset she was given injections of a gold compound for one year with moderate improvement. A second course of gold in 1952 was ineffective. Cortisone administration was then started and the patient improved moderately but developed hypertension, mild glycosuria, facial rounding, and hirsutism. After 4 months, cortisone was discontinued but the arthritis became quite severe and a second course was given in 1953. After 10 months the steroid was stopped again because the same side effects recurred and, in addition, a psychosis developed. In January, 1955, prednisone therapy was begun in dosage of 20 mg. daily. Psychosis and glycosuria did not recur but by the sixth month of therapy the blood pressure, which had been 124/76, rose to 176/120, purpuric spots appeared intracutaneously, and the patient complained of epigastric pain. Examination disclosed subcutaneous nodules, involvement of numerous joints, elevated ESR, a positive sheep cell agglutination test, negative L.E. cell test, and inversion of serum A/G ratio. X-ray of joints revealed osteoporosis, erosion of cartilage and destruction of subchondral bone. In the thirteenth month of therapy the steroid dosage was reduced to 17.5 mg. daily. During the sixteenth month of prednisone administration the patient developed severe paresthesias of both hands and feet, bilateral foot and wrist drop, left facial weakness of the central type, and subsequently anesthesia of upper and lower extremities. One week prior to death a Grade 2 systolic apical murmur appeared, together with pericardial and pleural friction rubs. Roentgenogram of chest revealed infiltrates in both lung fields and pleural effusion. There also appeared multiple, small, discrete, erythematous, nodular, cutaneous lesions. One of these nodules was biopsied and showed typical vascular lesions of polyarteritis nodosa. During her last day she complained of severe abdominal pain, appeared to have lost a large amount of blood, and died suddenly.

Necropsy was performed by Dr. Richard Swarm. Characteristic lesions of polyarteritis nodosa, old and recent, were present in synovial pannus of a sternoclavicular joint, striated muscle, nerve, skin, heart, liver, kidney, pancreas, and a small bronchus. The terminal episode was related to hemorrhage from an intrahepatic aneurysm. The other anatomic findings included focal interstitial myocarditis and valvulitis of the aortic and mitral leaflets.

Comment: This patient had rheumatoid arthritis, rheumatoid heart disease, and polyarteritis nodosa. The relationship of necrotizing arteritis to rheumatoid arthritis and to prednisone administration is discussed in another paper in this symposium.[20]

CASE 4.—D. W., a 55-year-old white woman, was admitted to the Clinical Center on April 26, 1955, with a diagnosis of rheumatoid arthritis. Onset occurred in 1939, many peripheral joints were involved and a spontaneous remission followed in 3 months. In 1950, while still in remission, the patient developed a myocardial infarction and the following year obstructive jaundice due to a stone in the common bile duct. The stone was removed surgically, and one month postoperatively the polyarthritis recurred. Subcutaneous nodules appeared near both elbows. Cortisone therapy was instituted (1951) and withdrawn 2 months later because edema developed. In 1954, phenylbutazone was administered and continued for one year. It was withdrawn because of digestive discomfort and nausea. Salicylates were given and moderate improvement followed but the patient found this unsatisfactory.

On admission the patient was found to have moderately severe, active rheumatoid arthritis, splenomegaly, and bilateral subcutaneous nodules. The lungs were clear. A soft blowing systolic murmur was heard over the left third interspace near the sternal border. X-ray of the chest showed moderate enlargement of the heart, exaggerated bronchovascular markings, and clear lung fields. Laboratory results included an elevated ESR, 2+ C-reactive protein, hematocrit of 31.5 per cent, A/G ratio 2.7/5.1 Gm. per cent, positive sheep cell agglutination test, negative L.E. cell test, and electrocardiographic evidence of intraventricular conduction defect.

On July 13, 1955, the patient developed congestive heart failure and what was considered to be pulmonary embolism of unknown origin. Digitalis and anticoagulant therapy were given and the patient recovered. Roentgenogram of chest was repeated and found to be normal. Prednisone administration was begun July 6, 1955. Moderate improvement followed and the patient was discharged on Nov. 5, 1955, receiving 20 mg. of prednisone daily. During the next few months the daily dosage was lowered to, and maintained at 17.5 mg. (at 15 mg. the arthritis flared). On April 22, 1956, an upper respiratory infection developed, associated with cough productive of white sputum; fever; night sweats; and malaise. The daily prednisone dose was raised to 20 mg. and Aureomycin was given. On May 3, she complained of occipital headache and 3 days later she was admitted to Baltimore Public Health Service Hospital. On admission it was observed that the arthritis had become acute. X-ray of chest revealed infiltration in the right mid-lung field. Sputum cultures failed to reveal acid-fast bacilli or other significant pathogenic organisms. Two blood cultures were negative. The cerebrospinal fluid was cloudy, contained 6 mg. per cent sugar and 5,200 leukocytes per cubic millimeter with 92 per cent polymorphonuclear cells. Culture of the fluid was sterile. Combined penicillin and streptomycin therapy was given. The patient failed to respond and died 48 hours after admission.

Necropsy was performed by Dr. Robert Katase at the Baltimore Public Health Service Hospital. The abnormal findings consisted of purulent leptomeningitis, purulent bronchopneumonia, adhesive pleuritis, old myocardial infarct and left ventricular aneurysm, thickened mitral and aortic valves, generalized arteriosclerosis, acute pyelonephritis, and acute salpingitis. Stains and cultures of tissues at autopsy (lymph nodes, brain, and lung) failed to demonstrate acid-fast bacilli.

Comment: This patient had rheumatoid arthritis and a past history of coronary thrombosis and common bile duct stone. Prednisone therapy in dosage of 17.5 mg. daily resulted in moderate improvement. During the tenth month of treatment, while at home, she developed an overwhelming intercurrent infection (purulent bronchopneumonia and meningitis) which did not respond to Aureomycin nor, during the last 2 days of life, to penicillin and streptomycin.

CASE 5.—M. H., a 64-year-old white woman, admitted to the Clinical Center on June 18, 1954, had polyarthritis of 5 years' duration and was now totally incapacitated. In 1950, and again in 1951, she received a 3-week course of cortisone therapy with moderate improvement and

VOL 5 195

no undesirable side effects. In 1952, hydrocortisone was injected into both knees, with some improvement. Examination in May, 1954, revealed multiple, bilateral, peripheral joint involvement and a blowing systolic apical murmur. Laboratory results indicated a moderate anemia, markedly elevated ESR, positive C-reactive protein test, positive sheep cell agglutination test, and a negative L.E. cell test. Glucose tolerance test indicated a diabetic pattern although glucose concentration in blood during fasting was normal. An electrocardiogram was normal. Roentgenograms of joints showed osteoporosis, destruction of cartilage and bone, and ankylosis of some articulations. Salicylate therapy was ineffective and while receiving salicylate the patient developed severe, bilateral episcleritis. Prednisone administration was begun on Dec. 28, 1954. The initial dosage was 30 mg. daily; the patient improved markedly and became ambulatory. The daily dose was reduced to 25 mg. on June 7, 1955. A duct cell carcinoma of the right breast was detected and a radical mastectomy was done on July 23, 1955. Wound healing (during prednisone administration) was poor despite multiple grafts. The daily dose of prednisone was lowered to 15 mg. by November, 1955. Paroxysmal tachycardia which developed at this time was controlled with aid of digitoxin and quinidine. Prednisone was discontinued (after gradual reduction of dose) on April 1, 1956, because of unsatisfactory healing of the surgical wound. Good healing followed promptly thereafter. In June, 1956, bilateral pneumonia (possibly pulmonary embolism) with pleural effusion and thrombophlebitis of the right iliac vein developed. Prednisone therapy was resumed on July 7, in doses of 5 mg. daily. The patient failed to respond, however, and developed congestive heart failure and paroxysmal auricular tachycardia. An electrocardiogram now revealed a right bundle branch block. The patient died in July, 1956.

Necropsy studies done by Dr. P. H. Geisler revealed rheumatoid heart disease with enlarged heart (500 grams), adhesive pericarditis, mitral and tricuspid valvulitis, interstitial myocarditis, and coronary arteritis. In the sciatic nerve a vascular lesion indistinguishable from polyarteritis nodosa was found; no other necrotizing lesions were present elsewhere. There was no evidence of metastatic carcinoma.

Comment: This patient with advanced rheumatoid arthritis of 7 years' duration had developed rheumatoid heart disease, congestive heart failure, pneumonia or pulmonary embolism, and pleural effusion. During the last year of life she also developed a carcinoma of the breast. The mastectomy wound failed to heal until prednisone was discontinued. At necropsy subacute vasculitis of coronary artery and necrotizing angiitis of the sciatic nerve were also detected. Prednisone was discontinued 4 months prior to death and was resumed in minimal dosage a few days before exitus. It is doubtful that steroid therapy was related to her death.

CASE 6.—J. S., a 70-year-old white man, was admitted to the Clinical Center on March 15, 1955, with a history of moderately severe polyarthritis that had persisted for 6 months and of weight loss of 41 pounds, during this period. Treatment with aspirin and colchicine had been ineffective. His past medical history was negative. Examination disclosed a well-nourished man who was incapacitated because of swelling, pain, and stiffness in the small joints of both hands and feet, both ankles and left knee. Subcutaneous nodules were present near the olecranon process bilaterally and the olecranon bursae were distended and warm. The cervical nodes were moderately enlarged. A soft, blowing, systolic murmur was heard at the apex. Laboratory studies revealed a markedly elevated ESR, 3+ C-reactive protein precipitate, strongly positive sheep cell agglutination test, and normal serum uric acid concentration. A glucose tolerance test was distinctly abnormal, the curve following a diabetic pattern; neither hyperglycemia nor glycosuria was present. X-rays of affected joints showed osteoporosis, cartilage and subchondral bone destruction.

Prednisone therapy was instituted on May 20, 1955; dosage which was initially 30 mg. daily was gradually reduced to 17.5 mg. At the higher dosage there was very marked improvement; at the lower dosage the arthritis flared. The disease could not be controlled with less than 25 mg. daily. The patient was discharged on July 8, 1955, moderately improved. During prednisone administration at the hospital neither hyperglycemia nor glycosuria had developed.

On Oct. 12, 1955, he was admitted to Mount Alto Veterans Administration Hospital.* Because the patient had developed diabetes, prednisone was withdrawn and the glycosuria disappeared. During the following weeks the patient became confused and his speech "garbled." He was totally incapacitated and was confined to bed and wheel chair. In January, 1956, lobar pneumonia developed. Antibiotics were given and prednisone was reinstituted. The pneumonia resolved and the steroid was again withdrawn (January 17), being replaced by salicylates. On March 3, 1956, the patient died suddenly while sitting in a wheel chair.

Necropsy was performed by Dr. John Howe of Mount Alto Veterans Administration Hospital. Acute and old cerebral infarcts with encephalomalacia, generalized atherosclerosis involving the coronary and cerebral vessels, bilateral pulmonary emphysema, hypertrophy of the right ventricle and passive congestion of the liver, and generalized rheumatoid arthritis were found. The stated cause of death was cerebral infarct.

Comment: This patient who was a potential diabetic developed overt diabetes when given prednisone. The severe mental confusion which supervened and the cerebral infarcts were most likely due to cerebral vascular atherosclerosis. It was the impression of the attending physician and the pathologist that the patient's death was due to recent cerebral infarct and not related to prednisone therapy.

SUMMARY

The precise relationship of molecular structure to biologic activity of 11, 17-oxygenated steroids has been described. Preliminary observations on the antirheumatic and electrolytic effects of new antirheumatic synthetic steroids have been cited.

The major portion of the paper has been devoted to a report of the serious adverse side effects of prednisone observed in a group of 39 patients with rheumatoid arthritis treated for periods extending up to 2 years. Special consideration has been given to the occurrence and management of peptic ulcers, pathologic fractures, polyarteritis nodosa, and mental disturbances complicating steroid therapy. Six deaths that occurred in this group have been analyzed in detail. The clinical reports and necropsy findings in each of these 6 cases have been summarized and briefly discussed.

CONCLUSIONS

Prednisone suppresses disease activity in rheumatoid arthritis effectively, promptly and almost uniformly. It is useful in properly selected cases and may control the disease when all other measures have failed. It must be used with caution and always as part of a comprehensive program of treatment. It has significant limitations and serious—at times fatal—adverse side effects. Hazards of long-term prednisone therapy increase alarmingly when the daily dosage exceeds 15 mg. Patients with rheumatoid arthritis whose disease cannot be satisfactorily controlled with a maintenance dose of 15 mg. of prednisone daily should be considered unsuitable for this type of therapy.

---

*We are indebted to Mount Alto Veterans Administration Hospital for permission to publish these data.

VOL.
5
1957

REFERENCES

1. Fried, J.: The Relation of Chemical Structure to Biological Activity of Adreno-Cortical Steroids, Bull. Rheumat. Dis. **6**:111, 1956.
2. Fried, J.: Biological Effects of 9-Alpha-Fluorohydrocortisone and Related Halogenated Steroids in Animals, Ann. New York Acad. Sc. **61**:573, 1955.
3. Liddle, G. W., Richard, J. E., and Tomkins, G.: Studies of Structure-Function Relationships of Steroids: The 2-Methyl-Corticosteroids, Metabolism **5**:384, 1956.
4. Glenn, E. M., Stafford, R. O., Lyster, S. C., and Bowman, B. J.: Relationship Between the Increased Biological Activity of Steroid Analogues and Their Rates of Inactivation in Rat Liver Enzyme Systems, paper quoted in Bull. Rheumat. Dis. **7**:129, 1957.
5. Bernstein, S., Allen, W. S., Littell, R., Feldman, L. I., Lenhard, R. H., Heller, M., Stolar, S. M., and Blank, R. H.: 16-Hydroxylated Steroids. IV. The Synthesis of the 16α-Hydroxy Derivatives of 9α-Halo-Steroids, J. Am. Chem. Soc. **78**:5693, 1956.
6. Thorn, G. W., Renold, A. E., Morse, W. I., Goldfien, A., and Reddy, A. B.: Highly Potent Adrenal Cortical Steroids: Structure and Biologic Activity, Ann. Int. Med. **43**:979, 1955.
7. Boland, E. W., and Headley, N. E.: Preliminary Clinical Trials With 9α-Fluoro Hydrocortisone Acetate in Rheumatoid Arthritis, Ann. Rheumat. Dis. **13**:241, 1954.
8. Black, R. L., Yielding, K. L., Peterson, R. E., Whedon, G. D., and Bunim, J. J.: Metabolic, Hormonal, and Antirheumatic Effects of Delta-1,9-Alpha-Fluoro-Hydrocortisone, Ann. Rheumat. Dis. **15**:76, 1956.
9. Villa, L., Sala, G., and Ballabic, C. B.: Clinical and Metabolic Effects of Δ^1-Dehydro-9-Alpha-Fluoro Hydrocortisone Acetate, Ann. Rheumat. Dis. **15**:237, 1956.
10. Peterson, R. E.: Personal communication.
11. Hellman, L., Zumoff, B., Schwartz, M. K., Gallagher, T. F., Berntsen, C. A., and Freyberg, R. H.: Antirheumatic and Metabolic Effects of a New Synthetic Steroid, paper quoted in Bull. Rheumat. Dis. **7**:130, 1957.
12. Bunim, J. J., Pechet, M. M., and Bollet, A. J.: Studies on Metacortandralone and Metacortandracin in Rheumatoid Arthritis, J.A.M.A. **157**:311, 1955.
13. Bollet, A. J., Black, R., and Bunim, J. J.: Major Undesirable Side-Effects Resulting From Prednisolone and Prednisone, J.A.M.A. **158**:459, 1955.
14. Bunim, J. J., Ziff, M., and McEwen, C.: Evaluation of Prolonged Cortisone Therapy in Rheumatoid Arthritis. A Four-Year Study, Am. J. Med. **18**:27, 1955.
15. Howell, D. S., and Ragan, C.: The Course of Rheumatoid Arthritis During Four Years of Induced Hyperadrenalism (IHA), Medicine **35**:83, 1956.
16. Quarton, G. C., Clark, L. D., Cobb, S., and Bauer, W.: Mental Disturbances Associated With ACTH and Cortisone: A Review of Explanatory Hypotheses, Medicine, **34**:13, 1955.
17. Glaser, G. H.: Psychotic Reactions induced by Corticotropin (ACTH) and Cortisone, Psychosom. Med. **15**:280, 1953.
18. Kern, F., Clark, G. M., and Lukens, J. G.: Peptic Ulceration Occurring during Therapy for Rheumatoid Arthritis. To be published.
19. Boland, E. W.: Prednisone and Prednisolone Therapy in Rheumatoid Arthritis, J.A.M.A. **160**:613, 1956.
20. Sokoloff, L., and Bunim, J. J.: Vascular Lesions in Rheumatoid Arthritis, J. CHRON. DIS. **5**:668, 1957.
21. Hench, P. S., and Ward, L. E.: Rheumatoid Arthritis and Other Rheumatic or Articular Diseases, in: Medical Uses of Cortisone, edited by F. D. W. Lukens, New York, 1954, Blakiston Company.
22. Stafford, R. O., Barnes, L. E., Bowman, B. J., and Meinzinger, M. M.: Glucocorticoid and Mineralocorticoid Activities of Δ^1-Fluorohydrocortisone, Proc. Soc. Exper. Biol. & Med. **89**:371, 1955.
23. Dulin, W. E.: Anti-Inflammatory Activity of Δ^1, 9α-Fluorohydrocortisone Acetate, Proc. Soc. Exper. Biol. & Med. **90**:115, 1955.

"BACK TO WORK" PROGRAM FOR PHYSICALLY HANDICAPPED ARTHRITICS

ROBERT H. MANHEIMER, M.D.,* AND MARTIN ACKER, B.S.**

NEW YORK, N. Y.

(Received for publication Feb. 5, 1957.)

INTRODUCTION

IN 1953, the New York State Chapter of the Arthritis and Rheumatism Foundation, together with the Institute for the Crippled and Disabled, instituted a "Back to Work" program for patients whose jobs had been lost or jeopardized because of a rheumatic disease. The program aids these patients in obtaining competitive employment consistent with their physical limitations.

Further, through the "Back to Work" program, the Chapter also sought information on several points: whether the number of patients who can use vocational rehabilitation warrants such a program; whether a rheumatic disease such as rheumatoid arthritis essentially precludes the patient's return to self-support; the best case-finding techniques; the services required by the patients to achieve self-support, their duration and their availability in the community; and whether appropriate employment can be found. Finally, the Chapter sought to learn whether patients, once placed, can sustain employment over a period of time.

Presented here are the results of the program's first three years of experience, and tentative answers to some of the questions stated above. Analysis of the patient's ability to sustain employment over a period of time will be made in a subsequent report.

METHOD OF OPERATION

Referrals.—Arthritis clinic staffs and private physicians were invited to refer candidates for the "Back to Work" program. As the program became known, some patients presented themselves and others came at the suggestion of non-medical agencies.

Requirements.—A physician's letter stating the patient's diagnosis, functional restrictions, and ability to tolerate regular daily work was requested with each referral. The referring sources were aware that the ability to use public transportation was important though not absolutely necessary and that the

*Medical Director, New York State Chapter, Arthritis and Rheumatism Foundation.

**Coordinator, "Back to Work" program, New York State Chapter, Arthritis and Rheumatism Foundation, and Institute for the Crippled and Disabled. Now at: Rehabilitation Service, Department of Preventive Medicine, Stanford University School of Medicine.

patients had to have sufficient interest to come to the Institute for interviews and the ability and persistence to attend the regular sessions of their rehabilitation programs.

The Services Offered.—The "Back to Work" program provides counseling, skill testing, refresher courses in old skills, training for new trades, and guidance in finding employment. The program is directed by a vocational counselor and draws upon the physical rehabilitation, testing, and training services of the Institute as needed. Other community resources such as the Division of Vocational Rehabilitation and the State Employment Service are also used. The patient's medical supervision remains with his clinic or private physician with whom the counselor keeps in touch throughout the patient's vocational rehabilitation. The program's services are discussed at greater length elsewhere.[1]

THE RESULTS

From September, 1953, through October, 1956, 268 patients were referred to the "Back to Work" Program. By November, 205 cases had been closed and 63 were active. Of the closed cases, 82 had returned to work, 41 had been rejected, and 82 had been accepted but had failed to return to work.

Each case record has been analyzed to determine the following facts: diagnosis, sex, age, duration of illness, functional handicap, period unemployed, length of rehabilitation services, and the referring agency. These facts were used to determine what relation, if any, they might have to the patient's success or failure in going back to work.

TABLE I. PATIENTS REFERRED, REJECTED, AND RETURNED TO WORK BY SEX, DIAGNOSIS, AND REFERRAL SOURCE

	REFERRED	REJECTED	WENT BACK TO WORK	
			NUMBER	PER CENT OF REFERRALS
Total	205	41	82	40
Sex				
Male	101	14	44	44
Female	104	27	38	37
Diagnosis				
Rheumatoid:	138	23	58	42
Arthritis	118	19	50	
Spondylitis	20	4	8	
Other:	67	18	24	36
Osteoarthritis	28	5	8	
Other rheumatic diseases	35	10	16	
Unknown	4	3	0	
Referral Source				
Medical:	105	16	48	46
Arthritis clinics	90	12	39	
Private physicians	15	4	9	
Nonmedical:	100	25	34	34
Self	60	11	22	
Other agencies	40	14	12	

Sex.—As shown in Table I, the patients were almost evenly divided as to sex. More women than men were rejected in the initial screening. Once accepted for vocational rehabilitation, there was no appreciable sex distinction in the ability to return to the labor market.

Age.—The patients ranged in age from 18 to the late sixties, just over half being between 40 and 59 years of age. Attention may be called to the fact that, even among those aged 60 or more, 25 per cent returned to work. (Fig. 1.)

Age of Patients

Related to Success or Failure in Going Back to Work

205 Patients

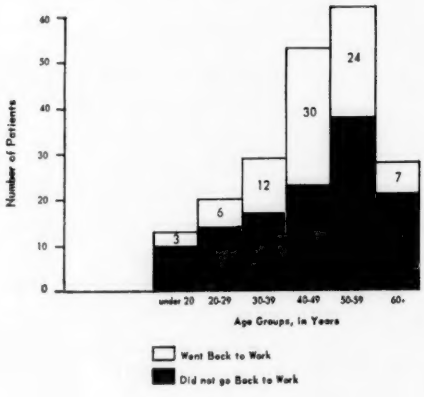

Fig. 1.

Diagnosis.—As Table I indicates, 118 of the patients had rheumatoid arthritis and 20 had spondylitis, while 28 suffered from osteoarthritis. In addition, 35 had other rheumatic diseases, including gout, bursitis, hemophilic arthritis, rheumatoid iritis, etc. Four cases had no diagnosis; three of these were rejected and the fourth withdrew before his medical record was received.

A somewhat larger proportion of successful cases was found among the rheumatoid and spondylitic patients than among those with other diagnoses.

Duration of illness.—At referral, 101 patients had been ill less than 10 years and 87 for from 10 to over 20 years. In 17 cases, the duration of the illness was not accurately determined.

As shown in Fig. 2, patients whose illness had lasted from 5 to 9 years included a somewhat higher proportion (47 per cent) who succeeded in returning to work than did the group as a whole (39 per cent). It might be noted that, of the 28 patients ill for 20 years or more, 11 went back to work.

Functional Handicap.—Ninety-four patients were examined by Institute physiatrists. From these medical reports, estimates were made of each patient's physical limitations, in terms of three major functions: (1) hand and arm activities; (2) standing, walking, and climbing activities; and (3) lifting activities.

These functions were classified either as normal (including slightly restricted) or as moderately to severely restricted.

The classification was based on the physician's eva'uation of the patient's ability to perform and was unrelated to physical changes. For example, patients classified as "normal to slightly restricted" might present gross deformity and yet be capable of adequately performing all three major functions.

Eighty of the 94 patients were found to have moderate to severe restrictions of at least one major function; half of these patients returned to work, as indicated in Fig. 3. The 29 patients who were restricted in all three major functions included 13 who obtained work as a consequence of the "Back to Work" program.

VOL.
5
1957

Duration of Illness

Related to Success or Failure in Going Back to Work

188 Patients*

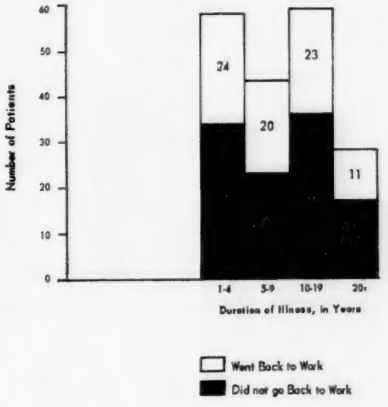

Fig. 2.

*The 205 referrals also included 17 patients for whom the duration of illness was not determined exactly.

Employment Status.—With respect to their experience in the labor market, the patients fall into three groups. The majority (141 patients) had been regular wage earners but were out of work when they came to the program.

Fig. 4 indicates the results obtained with this group of patients. Half of those unemployed for less than a year and almost a third of those out of work for 10 years or more succeeded in resuming self-support.

The other patients included 43 housewives and patients with juvenile rheumatoid arthritis (Still's disease) who had no substantial work experience (of whom 11 succeeded in going to work); and 21 patients who were employed but reported that their ability to continue working was jeopardized by their arthritis. Thirteen of these either obtained new jobs or made satisfactory adjustments to the jobs they held at referral.

Duration of Rehabilitation Services.—Thirty-seven per cent of the patients (including most of those rejected) spent less than 8 weeks in the "Back to Work" program, while, for half the group, rehabilitation lasted from 2 to 11 months. As shown in Fig. 5, only a small number of patients required assistance for as long as 12 months; two-thirds of these succeeded in going back to work.

Restrictions of Function: Hand and Arm; Ambulation; Lifting
Related to Success or Failure in Going Back to Work
94 Patients*

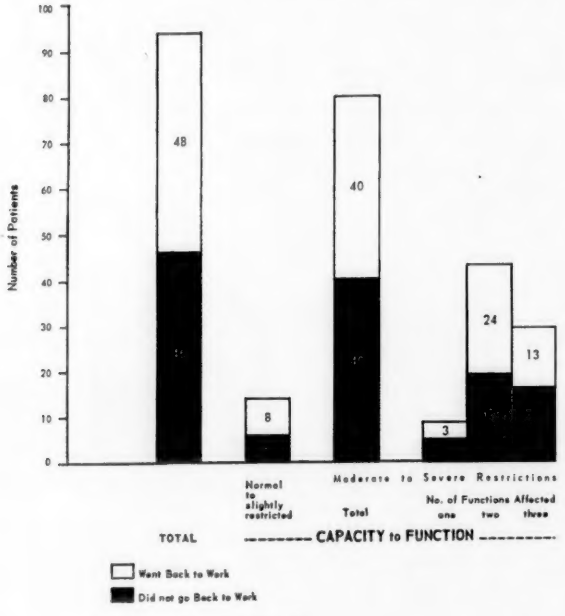

Fig. 3.

*Based on reports by Institute physicians, which were performed for 94 of the 205 patients.

Referral Sources.—Just over half the patients were "medically referred" (by arthritis clinics or private physicians); the others were referred by nonmedical agencies or were self-referred (Table I). In comparison with the latter, the medically-referred patients included fewer who were rejected and more patients who went back to work.

Employment.—The 82 jobs obtained by the successful patients ranged from unskilled industrial labor to professional work. Thirty-one patients got clerical employment, 29 went into industrial jobs, 18 obtained work in other categories, and 4 were placed in sheltered workshops.

Clerical jobs included switchboard operating, receptionist, bookkeeping, billing, accounting, filing, typing, and the operation of other office machines. Patients who entered industry took such jobs as optical worker, jeweler, leather worker, sewing machine operator, metal worker, and subcontract inspector.

Of the 82, 39 patients entered new trades while 43 returned to work with which they were familiar.

Starting wages averaged from $40 to $45 and ranged as high as $110 per week. Several patients have earned wage increases and promotions but, as noted above, a report on the postclosure experience of these people awaits further study.

The Unsuccessful Cases.—In the initial screening, 41 patients were rejected, 20 because they appeared able to utilize normal avenues to employment, 13 for physical reasons, 5 for emotional problems, and 3 for age.

Eighty-two of the 164 accepted patients failed to return to work. These included 31 who were dropped because they did not progress in the program due to physical or emotional handicap. Another 33 withdrew, often for unstated reasons. The remaining 18 received a variety of constructive services such as transfer to college or technical school or referral to other agencies (e.g., a school for the blind for a patient with rheumatoid iritis). Although immediate employment goals could not be projected for most of these 18 patients when they entered the program, some of them may be expected to get work in the future.

VOL.
5
1957

Duration of Unemployment

Related to Success or Failure in Going Back to Work

141 Patients*

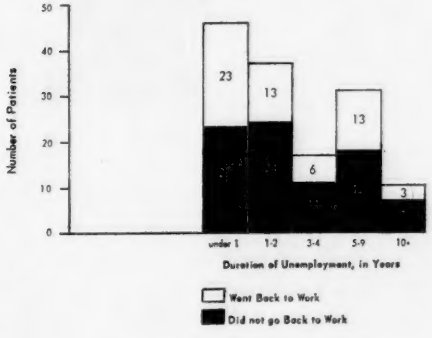

Fig. 4.

*One hundred and forty-one patients with previous work histories were unemployed at referral. In addition, the 205 referrals included 43 without regular work histories (housewives and students) and 21 employed patients.

DISCUSSION

General Findings.—The experience of the "Back to Work" program suggests the following answers to questions posed by the Chapter at the outset. The need for vocational rehabilitation of arthritic patients is evidenced by the steady pace of referrals, which required expansion of the program's staff. The types of service needed are substantially those originally envisaged, e.g., guidance of a vocational counselor, skill testing, training, physical therapy, self-help devices, and more intensive placement aid than is offered by commercial employment

agencies. The time required for vocational rehabilitation varies; half the patients remained in the program for less than 6 months and the great majority for less than 12. Finally, employment opportunities were found even for the seriously handicapped.

This experience further suggests that any representative group of ambulatory arthritics is likely to include a number of employable, but unemployed, patients; as has also been found in another study.[2] About two-fifths of these would resume self-support if given appropriate help. In addition, although several case-finding techniques are useful, a medical referral appears to be advantageous.

Duration of Rehabilitation Services

Related to Success or Failure in Going Back to Work

205 Patients

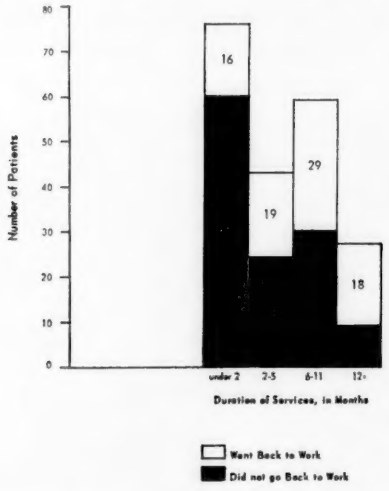

Fig. 5.

Criteria for Selecting Patients.—Criteria for the selection of appropriate candidates for vocational rehabilitation cannot be specifically defined at this time. However, the following general indications may be useful.

Serious functional impairment does not, of itself, preclude a return to competitive employment provided the ability to tolerate regular work is present. Obviously, bedridden and housebound patients must be excluded.

Despite the feeling in some quarters that rheumatoid patients are poor vocational rehabilitation risks, rheumatoid and spondylitic patients will probably be equally good as those with other rheumatic diseases. This was also suggested by Ragan's findings in a survey of the work records of 100 of his rheumatoid clinic patients.[3]

A majority of the patients in need of vocational rehabilitation are likely to be middle aged (70 per cent of those referred to the "Back to Work" program were at least 40 years old). Middle age does not prove a serious handicap and even patients over 60 may occasionally be placed on jobs.

Duration of disease up to 20 years should not greatly influence the patient's ability to return to work, and even 20 years of illness does not always prevent success.

Patients who have been unemployed less than one year will be promising candidates but even for those out of work more than 20 years a resumption of self-support is a possibility.

Therefore, in selecting patients for vocational rehabilitation, though a medical referral seems preferable, no single factor stands out sharply as a criterion. Motivation, or the part played in selection by the patient himself, however, is quite important. Not all patients referred to the "Back to Work" program presented themselves even for an initial interview and, in some cases, considerable time elapsed between the referral and the patient's appearance. The requirement that the patient should, of his own volition, cross the Institute's threshold doubtless screened out patients who (though otherwise capable of rehabilitation) were unwilling to consider returning to work, and this was, therefore, an important factor in selection. Timidity on the patient's part, however, need not be given too much weight. Once a patient displayed just enough initiative or, perhaps, curiosity to present himself to the "Back to Work" program, it was found that his interest in returning to work could often be strengthened to the point of success.

The Vocational Counselor.—The vocational counselor's contribution to the success of a rehabilitation program derives from his close and continuing contact with the patient, his understanding of the physical requirements of industrial tasks, his familiarity with the local labor market, and his skill in selecting and timing the phases of the individual patient's rehabilitation program so as to maintain the optimal rate of progress.

Thus, the counselor learns what the patient's work experience is; what he would like to do; and his anxieties about getting back to work. The latter may include fear that he cannot keep up with a healthy worker's production; concern lest prospective employers be prejudiced against a cripple; or self-consciousness about his handicap. The counselor helps the patient to realize that the trial job he is doing in the Institute's protected setting will develop his skills until they are on a par with those required by industry, that conscientiousness plus skill may be worth more to an employer than full physical fitness.

In directing the patients' course through the "Back to Work" program the counselor decides which patients merely require help in locating an employer who will hire a physically handicapped but competent worker. He may decide that another patient needs practice at his regular trade before competing with healthy job applicants. Finally he identifies the patients who require testing, practice work on different types of job, and possibly training in a new trade before they attain competitive status and are ready to seek work.

Vis-à-vis the potential employer, the counselor acts as the "honest broker." His professional understanding of the physical demands, motions, duties, output, and speeds required by commercial and industrial jobs and his knowledge of the individual patient's abilities and performance, enable him to convince the potential employer that the applicant's capacities, health, and experience are such that he can compete satisfactorily with nonhandicapped workers.

VOL.
5
1957

CONCLUSION

In 38 months, the cases of 205 candidates for vocational rehabilitation had been closed, 63 remaining active. Of the 205 closed cases, 41 (20 per cent) were initially rejected, 82 (40 per cent) failed, and 82 (40 per cent) returned to work, all but 4 in competitive industry.

Among 94 patients whose functional limitations were measured, 48 returned to work. Eighty of these 94 had moderate to severe restrictions in one or more of three major functions: hand and arm activities, ambulation, or lifting; forty of these 80 went back to work. The 29 patients with moderate to severe limitations in all three functions included 13 who returned to work.

REFERENCES

1. Acker, M.: Vocational Rehabilitation of Patients With Rheumatic Diseases, Arch. Phys. Med. **37**:743, 1956.
2. Ostrow, E. K.: The Effect of Arthritis on the Life Adjustment of a Group of Arthritis Clinic Patients, New York, 1955, State of New York Chapter, Arthritis & Rheumatism Foundation, p. 33.
3. Ragan, C.: Keeping the Patient With Rheumatoid Arthritis Employable, Indust. Med. **22**:309, 1956.

Erratum

In the paper by Richards, Bland, and White, "A Completed Twenty-five-Year Follow-up Study of 456 Patients With Angina Pectoris," published in the October, 1956, issue of the JOURNAL (Vol. 4, No. 4, pages 423-433), there is a transposition of material in Tables V and VI, page 430. The headings of the tables are correct, but the data of Table V refer to survival ratios and those in Table VI to actual proportions surviving. It is clear that survival ratios must, in general, be higher than crude proportions surviving.

On page 428, Dr. Hugo Muench should be given as Professor of Biostatistics at the Harvard School of Public Health, not the Medical School.

VOL.
5
1957